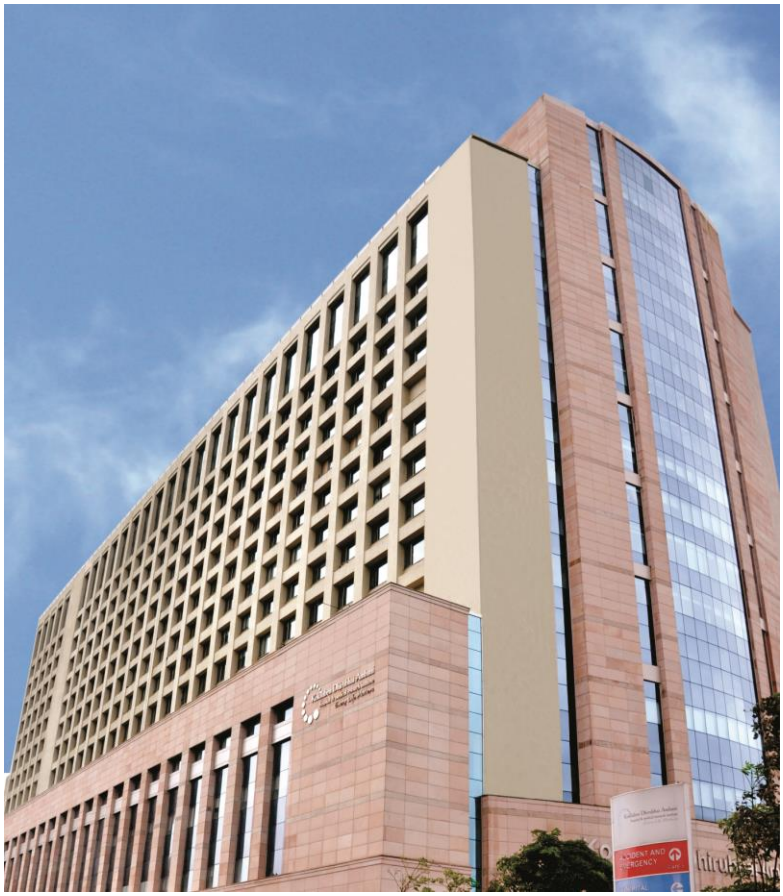

Kokilaben Dhirubhai Ambani
hospital & medical research institute

Every Life Matters

Medical Research Department (MRD)

Standard Operating Procedure (SOP)

Version No.: 04

SOP MRD INDEX

Medical Research Department (MRD)

Standard Operating Procedure (SOP)

	NAMES	DESIGNATION	SIGNATURE	DATE
PREPARED BY	Dr. Heena Gandhi	Senior Medical Research Associate	Gandhi	07/Aug/18
REVIEWED BY	Dr. Vijaykumar Gawali	Senior Manager - Clinical Research	V. Gawali	11/Aug/2018
APPROVED BY	Dr. Ram Narain	Executive Director		13/Aug/2018

SOP VERSION: 04

EFFECTIVE DATE: 21-August-2018

KOKILABEN DHIRUBHAI AMBANI HOSPITAL MUMBAI

Synopsis of amendments to SOP Version 03

Administrative Amendment: Institutional Scientific and Ethics Board (ISEB) is replaced with Institutional Ethics Committee (IEC).

Amendment to MRD SOP Section 1.6:

After reviewing Executive Director will signs and date the SOP on the approval page of the SOP document. This date of approval is declared as the effective date from where by the SOP is implemented. **Changed to** "After reviewing Executive Director will signs and date the SOP on the approval page of the SOP document. Effective date of the SOP shall be from 5 working days post approval date by Executive Director."

Amendment to MRD SOP Section 2.3:

"Investigator should follow Gazette notification dated 3rd July 2014, which states that Clinical Trials of Medical Devices is different in nature as compared to that of Drugs or Vaccines. In case of Medical Devices, there is no concept of conducting Phase I Clinical Trial to assess safety, tolerability of the Medical Devices. However, in pursuant to the decision of the Ministry of Health & Family Welfare, it has been decided that the procedures for the Clinical Trials approval, accreditations of Investigators, sites, Ethics Committee and such other conditions would be similar to the Clinical Trails of New Drugs/Vaccines." Above paragraph is replaced with below mentioned paragraph "Investigator should follow Gazette notification dated 31st January 2017 GSR 78(E), for Clinical Trials of Medical Devices."

Added following Paragraph under MRD SOP Section 2.3

- **Post-trial access of investigational new drug or new drug.-** Where any investigator of a clinical trial of investigational new drug or new drug has recommended post-trial access of the said drug after completion of clinical trial to any trial subject and the same has been approved by the Ethics Committee , the post-trial access shall be provided by the sponsor of such clinical trial to the trial subject free of cost, -

  (i) if the clinical trial is being conducted for an indication for which no alternative therapy is available and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator; and
  (ii) the trial subject or legal heir of such subject, as the case may be, has consented in writing to use post-trial investigational new drug or new drug;

and the investigator has certified and the trial subject or his legal heir, as the case may be, has declared in writing that the sponsor shall have no liability for post-trial use of investigational new drug or new drug.

- **Academic clinical trial.-**(1) No permission for conducting an academic clinical trial shall be required for any drug from the Central Licencing Authority where,-

(i) the clinical trial in respect of the permitted drug formulation is intended solely for academic research purposes including generating knowledge, knowing mechanism, advancement of medical science, determination of new indication or new route of administration or new dose or new dosage form; and
(ii) the clinical trial referred to in clause (a) has been initiated after prior approval by the Ethics Committee ; and
(iii) the observations generated from such clinical trial are not required to be submitted to the Central Licencing Authority; and the observational of such clinical trial are not used for promotional purposes.

Amendment to MRD SOP Section 4.1.1:

"As per the requirement of ISEB, site will submit the total number of copies equivalent to the total number of Institutional Scientific and Ethics Board members prevalent at that tenure plus additional copy for Institutional Scientific and Ethics Board records. Site would keep one copy for site record." Above paragraph is replaced with below mentioned paragraph "As per the requirement of IEC, site will submit three hard copies and one soft copy are required to be submitted for Institutional Ethics Committee records. Site would keep one copy for site record."

Amendment to MRD SOP Section 4.1.3:

"The Principal Investigator will submit 1 copy of Annual Study Report and related documents." Above paragraph replaced with below mentioned paragraph "The Principal Investigator is required to submit 1 copy of Periodic Study Report and related documents every 6 months."

Synopsis of amendments to SOP Version 02

Amendment to MRD SOP Section 4.2.1 :

Regarding definitions mentioned above please also note, Investigator and concerned personnels also need to refer definitions mentioned by regulators.

Amendment to MRD SOP Section 4.2.3
Notify the Licensing Authority, the Sponsor or his representative and the Ethics Committee within 24 hours of their occurrence. The report of the serious adverse event of death and serious adverse event other than death, after due analysis shall be forwarded by the Investigator to Chairman of the Ethics committee and the chairman of the Expert committee constituted by the Licensing Authority with a copy of the report to the Licensing Authority and the head of the Institution where the trial has been conducted within fourteen calendar days of occurrence of the serious adverse event of death or other SAE.
Amended as : Notify the Licensing Authority, the Sponsor or his representative and the Ethics Committee within 24 hours of their occurrence. The report of the serious adverse event of death and serious adverse event other than death, after due analysis shall be forwarded by the Investigator to ISEB , Licensing Authority and the head of the Institution

where the trial has been conducted within fourteen calendar days of occurrence of the serious adverse event of death or other SAE.

Synopsis of amendments to SOP Version 01

MRD SOP Section 1.2, "Research Co-ordinator for MRD will"
Amended to "Medical Research Associate appointed for MRD will".

MRD SOP Section 1.6, "Research Co-ordinator"
Amended to "Medical Research Associate".

MRD SOP Section 1.6, One complete original set of current SOPs will be filed centrally in the SOP Master file, by Research Co-ordinator in MRD Dept.
Amended to, One complete original set of current SOPs will be filed centrally in the SOP Master file, by Medical Research Associate in MRD Dept.

MRD SOP Section 2,
Meet all the qualifications specified by the applicable regulatory requirement(s). Current medical practitioner registration details and similar documentation should be referenced in the CV.

Amended to, Meet all the qualifications specified by the applicable regulatory requirement(s). Current medical practitioner registration details (if applicable) and similar documentation should be referenced in the CV.

New amendment to MRD SOP Section 2,
Following paragraph added:
Investigator should keep himself/herself updated with regulatory amendments as in force from time to time. Investigator must update the entire team about this information. Investigator and the study team must follow these amendments as per the instructions of CDSCO office and concerned regulatory authorities.

New amendment to MRD SOP Section 2.3
Following paragraphs added:
Investigator should follow Gazette notification dated 3rd July 2014, which states that , the number of clinical trials an Investigator can undertake should be commensurate with the nature of the trial, facility available with the Investigator etc. However, under no circumstances the number of trials should be more than three at a time.

Investigator should follow Gazette notification dated 3rd July 2014, which states that Clinical Trials of Medical Devices is different in nature as compared to that of Drugs or Vaccines. In case of Medical Devices, there is no concept of conducting Phase I Clinical Trial to assess safety, tolerability of the Medical Devices. However, in pursuant to the decision of the Ministry of Health & Family Welfare, it has been decided that the procedures for the Clinical Trials approval, accreditations of Investigators, sites, Ethics Committee and such other conditions would be similar to the Clinical Trails of New Drugs/Vaccines.

Investigator should follow Gazette notification dated 3rd July 2014, which states that, as mentioned in the report, Placebo- Controlled trials are fairly uncommon these days, although there will be a case for such trials in special circumstances. Since other remedies are usually available, the drug to be tested is considered to the existing therapy. There is thus no reason to deprive a patient of a drug in such placebo controlled trial. The Pharmaceutical companies, the Investigators, the Drugs regulator and the ECs all would have to ensure that the design used in a placebo controlled trials is appropriate, efficient and ethical.

- Investigator should follow Gazette notifications with respect to injury to the participating patients and compensation.

Amendment to MRD SOP Section 4.2.3,
Following paragraph added:
"In case the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event."

Notify the Licensing Authority, the Sponsor or his representative and the Ethics Committee within 24 hours of their occurrence. The report of the serious adverse event of death and serious adverse event other than death, after due analysis shall be forwarded by the Investigator to Chairman of the Ethics committee and the chairman of the Expert committee constituted by the Licensing Authority with a copy of the report to the Licensing Authority and the head of the Institution where the trial has been conducted within ten calendar days of occurrence of the serious adverse event of death or other SAE.

Amendment to MRD SOP Section 4.2.3,
Following paragraph is deleted:
Report all local SAEs to the sponsor within 24 hours of being informed about the event, by telephone and/or fax, according to the sponsor's specified reporting procedures and instructions. Follow up with additional information as soon as it becomes available.

Amendment to MRD SOP Section 5.1
Following paragraph added:
As per new amendments in Schedule Y by DCGI office via Gazette Notifications, site should follow, (iv) An audio-video recording of the informed consent process of individual subject, including the procedure of providing information to the subject ad his understanding on such consent, shall be maintained by the investigator for record.",

Amendment to MRD SOP Section 5.8
Audio -Video Consenting Guidance Document version: 1 dated 15 Jan 2014, was used at the site a separate document, but it is added as part of MRD SOP Version 02.

SOP NO.01/04 :-PREPARING SOP

1.1 : Purpose :-

The purpose of this Standard Operating Procedure (SOP) is to define the process for writing, reviewing, distributing and amending SOPs of Medical Research Department (MRD) in Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute (KDAH)

The SOPs provide clear, unambiguous instructions so that the related activities of the Medical Research Department are conducted in accordance with:-

- Schedule Y (Drugs and Cosmetic Act 1940; amendment 20th January 2005),
- ICMR's Ethical Guidelines for Biomedical Research on Human Participants (2006), Indian GCP Guidelines (2001),
- WHO Operating Guidelines for Ethical Review Committee that Review Biomedical Research (2000)
- The International Conference on Harmonization - Good Clinical Practices (ICH-GCP) Guidelines (1996).
- Declaration of Helsinki and

1.2 : **Medical Research Associate appointed for MRD will :-**

- Co-ordinate activities of writing, reviewing, distributing and amending SOPs
- Maintain on file all current SOPs and the list of SOPs
- Maintain on file all past SOPs of MRD.
- Assist Head MRD to formulate an SOP .
- Propose new/ modified SOPs as needed
- Select the format and coding system for SOPs
- Draft the SOP in consultation with the Head MRD and involved administrative staff
- Review the draft SOP
- Submit the draft for final review to Head MRD

1.3 : Executive Director will :-

- Approve the SOPs
- Sign and date the approved SOPs

1.4 : Identify the need for new or amending SOP :-

Any Principal Investigator, Sub-Investigator, Study Co-ordinator, KDAH Doctor or any member of study team would like a revision or notices an inconsistency/ discrepancy / has any suggestions on how to improve the existing SOPs or requests to design an entirely new SOP can put forth his/ her request.

1.5 : Format and layout :-

Each SOP should be given a number and a title that is self-explanatory and is easily understood. A unique code number with the format

SOP aa / bb: will be assigned to each SOP item by the Research Co-ordinator

aa will be a two-digit number assigned specifically to that SOP.
bb will be a two-digit number identifying the version of the SOP

The number of version should be started from 01 hence for example, SOP01/01 is the SOP number 01 with version 01.

1.6 : New SOP :-

When the need for a new SOP has been identified and agreed on, a draft will be written by a Medical Research Associate.

After incorporating the suggestions put forth the copy of the revised draft SOP will be circulated to the personnel who has suggested amendment in SOP.

The suggestions agreed upon unanimously, by the personnel who has suggested amendment, will be incorporated in the revised draft SOP and the final draft SOP will be formulated.

After reviewing Executive Director will signs and date the SOP on the approval page of the SOP document. Effective date of the SOP shall be from 5 working days post approval date by Executive Director.

The approved SOPs will be implemented from the effective date.

When the revised version is distributed to the concerned personnel, one copy of the earlier version will be placed in the file entitled ‘Past SOPs of MRD.

One complete original set of current SOPs will be filed centrally in the SOP Master file, by Medical Research Associate in MRD Dept.

SOP NO.02/04 :- SOP for Training study team in MRD and their responsibilities.

The Principal Investigator (PI) is ultimately responsible for protocol-specific staff training, as well as ensuring that he/she has adequately-trained staff to conduct the study. The investigator is responsible for facilitating the training of his/her clinical research team. However, the clinical research staff members have a professional responsibility to obtain and maintain the knowledge and skill sets necessary to perform their clinical research related duties. This SOP applies to all study participants.

The investigator(s) should:

- Maintain an up-to-date *Curriculum vitae*.

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial. This should be evidenced in the CV.

- Meet all the qualifications specified by the applicable regulatory requirement(s). Current medical practitioner registration details (if applicable) and similar documentation should be referenced in the CV.

- Provide evidence of such qualifications through up-to-date *Curriculum vitae* and/or other relevant documentation requested by the sponsor, or the regulatory authority(ies).

- Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties. The list is in the form of a Delegation Log and delegated duties should be captured and signed and dated by the investigator on a per person basis. The delegation log may be provided by the Sponsor but for investigator-initiated research studies (IIRS), a separate site log should be developed.

- Investigator should keep himself/herself updated with regulatory amendments as in force from time to time. Investigator must update the entire team about this information. Investigator and the study team must follow these amendments as per the instructions of CDSCO office and concerned regulatory authorities.

2.1 : Training in Good Clinical Practice and other required trainings : -

1. GCP training and education are recommended for clinical research team members, especially the PI and Clinical Research Coordinator and also any member of the clinical research team with a significant role in the conduct of a clinical research study must be knowledgeable in GCP.

2. If the investigational site is conducting a study under an Investigational New Drug (IND) Application with the US Food and Drug Administration (FDA), a form FDA1572 must be completed. The site must be knowledgeable in and comply with the FDA regulations. The FDA has the authority to inspect any foreign or US-based clinical trial site to ensure compliance with the regulations.

3. Standard operating procedures (SOPs) describe the processes that must be followed when conducting clinical research studies in human participants. SOPs are based on the international guidelines and regulations governing clinical research, as well as the policies and procedures of the KDAH.

2.2 : Documentation of training received :-

Clinical Research Personnel should be prepared to demonstrate all training received and CVs should be updated as required. It is recommended that an assessment of the employee's knowledge of the regulations and guidelines be conducted upon hiring and on a regular basis. It is recommended that an assessment of any additional protocol-specific skill requirements be conducted prior to activation of each new protocol.

2.3 : Responsibilities of PI :-

- PI should have sufficient time to properly conduct and complete the trial within the agreed trial period and have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

- PI should ensure that documentation of this training be kept current and available for review on request throughout the entire trial period.

- PI should ensure that tasks delegated to study staff are documented appropriately. This can be evidenced by the delegation log. However, study specific training records should be maintained to provide evidence that tasks were delegated following the correct training.

The Principal Investigator(s):

• should ensure that clinical studies are carried out according to International Conference on Harmonisation (ICH), ICMR GUIDELINES SCHEDULE-Y GUIDELINES regulatory authorities requirements and any other local requirements.

• ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions. An initiation meeting may be held where all required staff are present and written evidence of study specific training is developed.

• has the authority to delegate duties to other qualified clinical research staff members, PI assumes ultimate responsibility for the overall conduct of a clinical research study and for compliance with all applicable regulations and guidelines. The PI must document the delegation of tasks/duties. And also should ensure that they are appropriately qualified to conduct the trial. PI is also responsible to ensure an adequate number of qualified staff and adequate facilities,

• should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

- Must declare any conflicts of interest, payments etc. from other parties.

- Must maintain a list of any delegated duties with respect to the trial, and the persons and qualifications of those persons to whom the duties are assigned.

- Must provide medical care to trial participants that is necessary as a result of any adverse events experienced during or following the trial that are related to the trial, and must be responsible for all trial-related medical decisions

- Must present all trial related documents to the IEC for review including the Investigator's Brochure as well as updates.

- Must possess, prior to trial commencement, approval from IEC, of trial protocol, patient information and consent documents, recruitment procedures, consent form updates and any other information given to subjects.

- Must ensure that the trial is conducted according to the approved protocol.

- Should take all efforts to avoid protocol deviations. Must document any deviation from the protocol and also must notify to IEC for review.

- Must ensure accountability of the investigational product at the trial site(s).

- Must ensure that subjects have made fully informed, written consent, with all trial procedures and risks adequately explained and that the principles and essential elements of Informed consent are up held and included in the information document;

- Should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor

- Should submit written summaries of the trial status to the IEC annually, or more frequently, if requested by the IEC.

- Should provide written reports to the sponsor, and the IEC promptly on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

- Should comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IEC.

- Should promptly inform the trial subjects If the trial is prematurely terminated or suspended for any reason as well as the institution and should assure appropriate therapy and follow-up for the subjects, and where required by the applicable regulatory requirement(s), inform the regulatory authority(ies).

- Investigator should follow Gazette notification dated 3rd July 2014, which states that, the number of clinical trials an Investigator can undertake should be commensurate with the nature of the trial, facility available with the Investigator etc. However, under no circumstances the number of trials should be more than three at a time.

- Investigator should follow Gazette notification dated 31st January 2017 GSR 78(E), for Clinical Trials of Medical Devices.

- **Post-trial access of investigational new drug or new drug.-** Where any investigator of a clinical trial of investigational new drug or new drug has recommended post-trial access of the said drug after completion of clinical trial to any trial subject and the same has been approved by the Ethics Committee , the post-trial access shall be provided by the sponsor of such clinical trial to the trial subject free of cost, -

  (i) if the clinical trial is being conducted for an indication for which no alternative therapy is available and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator; and
  (ii) the trial subject or legal heir of such subject, as the case may be, has consented in writing to use post-trial investigational new drug or new drug;

and the investigator has certified and the trial subject or his legal heir, as the case may be, has declared in writing that the sponsor shall have no liability for post-trial use of investigational new drug or new drug.

- **Academic clinical trial.-**(1) No permission for conducting an academic clinical trial shall be required for any drug from the Central Licencing Authority where,-

  (i) the clinical trial in respect of the permitted drug formulation is intended solely for academic research purposes including generating knowledge, knowing mechanism, advancement of medical science, determination of new indication or new route of administration or new dose or new dosage form; and
  (ii) the clinical trial referred to in clause (a) has been initiated after prior approval by the Ethics Committee ; and
  (iii) the observations generated from such clinical trial are not required to be submitted to the Central Licencing Authority; and the observational of such clinical trial are not used for promotional purposes.

- Investigator should follow Gazette notification dated 3rd July 2014, which states that, as mentioned in the report, Placebo- Controlled trials are fairly uncommon these days, although there will be a case for such trials in special circumstances. Since other remedies are usually available, the drug to be tested is considered to the existing therapy. There is thus no reason to deprive a patient of a drug in such placebo controlled trial. The Pharmaceutical companies, the Investigators, the Drugs regulator and the ECs all would have to ensure that the design used in a placebo controlled trials is appropriate, efficient and ethical.

- Investigator should follow Gazette notifications with respect to injury to the participating patients and compensation.

2.4 : Responsibilities of Clinical Research Coordinator and other team members:-

The clinical research coordinator (CRC) is a specially trained professional (nurse, health professional, or other qualified clinical research team member) who manages most of the day-to-day responsibilities of a clinical research study. The CRC works in collaboration with the PI and with a multidisciplinary research team to ensure that rigorous clinical research standards are maintained.

Responsibilities of the CRC include:

The specific roles of the CRC are described in the procedures of each SOP

• Works closely with the PI to plan, organize, and carry out the clinical research study in an efficient and timely manner.

• Adheres to the GCP guidelines, regulations, and standard operating procedures.

• Assesses the skills required for each protocol and obtains the necessary training.

• Acts as a liaison between the sponsor, IEC and other personnel.

• Also follow-up with patient.

• Coordinates all aspects of the clinical research study under the direction and delegation of the PI.

• Understands privacy and safety issues and their implication

SOP NO. 03/04 :- SOP for Site Selection , Site initiation, Site monitoring and site close out.

3.1 : Site Selection Visit
3.2 : Site Initiation Visit
3.3 : Site Monitoring Visit
3.4 : Site Close-out Visit

3.1. Site Selection Visit : -

The PI and the research team are responsible for supplying the required information to the sponsor.

3.1.1 : Responsibilities of Site :-

Site will take all efforts so that Sponsor would able to validate that the site is knowledgeable about GCP and all other applicable regulations.

- Site will confirm the meeting date with the sponsor and request an agenda for the visit
- Obtain and compile the necessary information and documents, as requested by the sponsor.
- Notify the appropriate departments of the visit (e.g., pharmacy, laboratory, and xray).
- Determine the areas that the sponsor will want to visit on the tour of the facilities.
- Distribute the protocol, investigator brochure and CRFs (if available) to the appropriate site staff for review.
- Compile a list of personnel that the sponsor may wish to contact.
- Identify the key clinical research staff that should attend, and arrange the most suitable meeting date, time and place.

Site will help sponsors to assess following : -

• Availability and qualifications of the site staff
• Investigator workload and conflicting studies

• Participant recruitment potential for the study

• Site staff communication and responsiveness (e.g., return of telephone calls, provision of documents in a timely manner).

• Clinical research study management procedures and processes (SOPs)

• Documents confirming training

• Ability to meet the required timelines

• Storage of confidential records

Site will keep record of a copy of the completed sponsor Site Selection Visit documentation (If sponsor has provided any such report.)

Site will review the Investigator's Brochure and any up-to-date information on the investigational product (If available). The Investigator(s) must be familiar with the product, including pre-clinical toxicology, pharmacology, pharmacokinetics and up-to- date clinical data if applicable.

3.1.2 On Site Selection Visit , Study Team will prepare following documents : -

1. Document the name, contact information and title of the sponsor representative.

2. Confirm that the Confidentiality Disclosure Agreement (CDA) has been signed.

3. Review the protocol and complete the study feasibility assessment requirements (e.g., sponsor questionnaires).

3.1.3 : During the Site Selection Visit : -

1. Meet with the sponsor representative(s) as scheduled to review the protocol and other applicable study documents according to the agenda.

2. Topics for discussion may include:

• Site staff comments or concerns with the protocol

• Discussion of IEC & MRD SOPs and ICH/GCP guidelines

• Patient population relative to the protocol inclusion and exclusion criteria

• Recruitment capabilities/strategies

• Timelines for protocol review and approvals

• Contract obligations

• Intellectual property and publication rights

3. Accompany the sponsor representative on a tour of the facilities. Areas visited may include:

• Applicable clinical areas and examination rooms
• Laboratories including fridges and freezers
• Pharmacy
• Work areas for the study staff
• Sponsor monitoring areas
• Storage areas for study drug and other study supplies

4. Request information from the sponsor, such as:

• Sponsor's overall research study management, monitoring, communication and data management plans
• Anticipated study timelines and dates, such as:
• Receipt of DCGI, FDA and other regulatory agency approvals
• Availability of other documents (e.g., draft contract/budget, CRFs, if not available at meeting)
• Investigator meeting
• Study start up plan.
• Timeline for overall study completion
• Site selection status and when it can be expected
• Any additional information that might be required by the sponsor.

3.1.4 : Site Selection Visit Follow-Up :-

1. Send any additional information/documents requested to the sponsor.

2. If the site is selected, site to complete following activities:
• Prepare the ethics submission package using IEC guidelines.
• Prepare a final study budget.
• Site review of study contract.
• Forward the Clinical Trail Agreement (CTA) , to Medical Research Department for review and institutional sign-off.

• Investigator sign-off of contract.

• Create the investigator study files. For industry-sponsored studies, the sponsor may provide the site with Investigator Study Files

3.2: Site Initiation Visit : -

3.2.1 : Preparing for the Site Initiation Visit : -

At the site initiation visit, the monitor or sponsor representative will conduct a final assessment of the site's readiness to start the clinical research study. He/she will focus on compliance with the protocol, applicable regulatory requirements and Good Clinical Practice (GCP) guidelines.

1. The staff scheduled to attend the site initiation meeting should conduct a comprehensive review of the protocol and other study information prior to the initiation visit. A list of study staff questions should be prepared.

2. Confirm that all required IEC documents are available.

3. Confirm that the clinical trial agreement (CTA), indemnification letter and budget are finalized and signed.

4. Request an agenda for the visit from the sponsor.

5. Confirm the clinical research staff that must attend and arrange the most suitable meeting date, time and place.

6. Notify appropriate departments of the visit (e.g., pharmacy, laboratory, and x-ray).

7. File all essential documents in study file (or sponsor-supplied Investigator Study File), and compile any outstanding documents to provide to the sponsor's monitor, or clinical research associate (CRA) at the initiation meeting.

3.2.2 : Protocol Training :-

1. Review the study procedures with the research staff assigned to the study. Site to request monitor or other sponsor representative to do protocol-specific skills assessment with the staff to determine any additional training needs to perform their study related duties.

2. If required, arrange for any additional training for research staff prior to the anticipated study start date.

3. Conduct training for support staff involved in the clinical research study (e.g., nurses, pharmacists, physicians, lab personnel), if applicable.

4. Inform all involved departments and team members of the site contact person responsible for the overall management of the clinical research study.

3.2.3 : During the Site Initiation Visit :-

The monitor may review the following items at the site initiation visit

1. Protocol:

• Study design, rationale, objectives, treatment plan and schedule
• Investigational product information and dose-modification plans
• Study-specific procedures and skill sets
• Participant eligibility criteria (inclusion/exclusion)
• Medical care and ongoing monitoring of research study participants
• Protocol amendments
• Multicentre study procedures
• Participant recruitment strategies and targets
• Process of informed consent
• Participant recruitment, enrolment, and tracking
• Participant withdrawal criteria and premature withdrawal procedures
• Safety issues
• Premature termination or suspension of the research study
• Final requirements of the investigator

2. IEC Interactions:

• Communication with IEC
• IEC approvals
• Ethical considerations relating to the research study
• IEC reporting requirements.

3. Study Resources:
• Adequate site resources (e.g., patient population, qualified staff, available equipment, adequate facilities) to conduct study

4. Laboratory Procedures:
• Supplies

• Sample collection, processing and shipping (or storage) requirements
• Local or central laboratory considerations

5. Safety Reporting:

• Safety information and reporting procedures
• Serious adverse event (SAE) reporting
• Unexpected adverse event (AE) reporting
• Adverse drug reaction (ADR) reporting
• Investigational new drug (IND) reports
• Sponsor contact

6. Investigational Product:

• Registration or randomization procedures and methods
• Supply, handling and storage of the investigational product
• Labeling of investigational product
• Investigational product/study drug accountability instructions
• Investigational product destruction procedures
• Unblinding procedures

7. Data Collection:
• Supply of case report forms (CRFs)
• Source documentation plans
• CRF completion and collection plans, including electronic CRFs (eCRFs)
• Overall data management plans

8. Records:

• Participant screening and recruitment logs
• Drug accountability/dispensing records
• Access requirements to source data/documents
• Data handling and record keeping
• Data retention issues

9. Monitoring:
• Monitoring procedures and timing
• Monitoring reports
• Site visit log
• Task delegation and site personnel logs

10. Contracts:

• Site and sponsor contract obligations
• CTA
• Indemnification agreement
• Site and sponsor financial obligations
• Payment schedule and tracking
• Publication policy

11. Regulatory and Compliance:
• Audit/inspection plans and procedures
• Good Clinical Practice (GCP) guidelines
• Quality Control (QC) and Quality Assurance (QA)
• Regulation review.

3.2.4 : Study Activation and Initiation Visit Follow-Up :-

In preparation for study activation:
1. Confirm that the sponsor sends a written summary of key discussions and agreements made during the site initiation visit. Follow up if necessary.

2. Confirm readiness of the site (e.g., staffing assignments, equipment, documents, study tools, protocol training) to start the study.

3. Confirm receipt of all study-related materials such as, CRFs, laboratory supplies, investigational product(s).

4. Distribute protocol summaries and worksheets, if not done previously (the sponsor may provide study-related worksheets, however the site may still elect to use their own).

5. Notify all appropriate departments that the study is ready to enroll participants.

6. Initiate study recruitment strategies and begin enrolling study patients/participant.

3.3: Site Monitoring Visit : -

3.3.1 : Communication with the Sponsor :-

The sponsor's clinical research associate (CRA) is usually the main contact between the sponsor and the investigator site and is also a key study resource for the site. The CRA must ensure that the research study is conducted and documented in accordance with the sponsor's requirements (e.g., written SOPs, protocol-specific requirements), as well as applicable regulations and guidelines. The investigative site staff and the CRA should maintain good and responsive communication.

1. Communicate as needed to ask questions or to inform the sponsor of any study related issues. Document important conversations (e.g., where key decisions or clarifications have been made) between the site and sponsor representatives.

2. Store communication between the sponsor and the site (e.g., letters, faxes, telephone records, emails) in the appropriate section of the investigator study files.

3.3.2 : Monitoring Visits :-

Frequency of monitoring visit would generally depend on type and complexity of the study, rate of enrollment, and site performance.

Site expects sponsors to conduct their first monitoring visit after 1 or 2 participants enrolled into the study.

Further monitoring visits would be confirmed on a visit-by-visit basis as the study progresses.

3.3.3 : Preparing for a Monitoring Visit :-

1. Site would request for agenda for monitoring and then mutually convenient date and time would be scheduled.

2. Site team would inform all relevant staff members and PI.

3. Working space for the CRA would be identified, which would allow to maintain confidentiality of records

4. Compile any outstanding documents and confirm that any previous action items have been addressed to the extent possible.

5. The applicable case report forms (CRFs) should be completed on a timely basis, and available for review, along with the corresponding source documents.

3.3.4 : During a Monitoring Visit :-

Site would be prepared to provide or verify the following during monitoring visits:

1. That investigator qualifications and resources and site facilities (e.g., laboratories, equipment, staff) remain adequate to safely and properly conduct the research study.

2. Current list of study personnel and delegation of tasks.

3. That the investigational product has been stored, handled, dispensed, and destroyed or returned according to the protocol and sponsor requirements.

5. That written informed consent was obtained before each participant's involvement in the research study and only eligible participants have been enrolled.

6. Participant recruitment logs are complete and original recruitment targets and timelines are reviewed.

7. The CRA will check the accuracy and completeness of the CRF entries, verify the source documents and other research-related records, and will inform the PI and/or the clinical research coordinator (CRC) of any CRF entry errors, omissions, or illegibility.

8. That the source documents and other research records and essential documents are accurate complete, kept up-to-date and filed appropriately.

9. That all serious adverse events (SAE's) have been reported within the time periods required by GCP, the protocol, the sponsor, IEC and the FDA (if applicable).

10. Where possible and applicable, that action has been taken to prevent the recurrence of protocol violations (if any) and/or deviations those were noted in previous communications by the CRA.

11. The visit of the CRA to the site will be documented for the site's records if not recorded by monitor.

3.3.5 : Monitoring Visit Follow-Up :-

The CRA will submit a written report (i.e., monitoring visit report) to the sponsor after each site visit or in-depth study-related communication. The site should receive a summary of the visit findings and any follow-up actions required.

1. Follow-up with the CRA to obtain a summary of the monitoring visit

2. Review the summary for significant findings and/or recommended actions.

3. Discuss plans for any subsequent visits.

3.4: Site Close out Visit: -

The same study closeout procedures should be followed if the sponsor discontinues a study in its entirety or at an individual site. In addition, the IEC should be informed promptly, and provided with the reason(s) for the discontinuance of the study.

3.4.1 : Preparation for Study Closeout :

When the last participant has completed the last scheduled study visit and the associated case report forms (CRFs) are completed, the clinical research associate (CRA) will initiate formal study closeout procedures.

1. If the sponsor requests an on-site closeout visit, request an agenda from the sponsor.

2. Determine the areas that the sponsor may want to visit, and notify the appropriate departments (e.g., pharmacy).

3. If applicable, communicate with the appropriate staff member so that a final inventory of the investigational product is conducted and final accountability records are completed and available.

4. Inform all relevant staff members (e.g., Clinical Research Coordinator, Principal Investigator) and schedule a mutually convenient date and time for closeout procedures.

5. Book a room, if appropriate, with adequate working space for the CRA that also allows for the confidentiality of records to be maintained.

6. Strive to compile all outstanding documents and confirm that any previous action items have been completed to the extent possible.

7. Review the investigator study files for completeness and resolve any discrepancies (e.g., in a memo or note to file).

8. The remaining CRFs should be accurately completed and available for review/monitoring, along with the corresponding source documents.

9. Ensure that any outstanding CRF corrections, additions, or deletions are made, dated, explained (if necessary), initialed by the investigator or authorized delegate and ready for review, along with the corresponding source documents. In addition, ensure that all data queries received to date have been resolved.

10. Arrange for the PI to review and sign the completed CRFs, as applicable if not done previously.

11. Ensure that all details in the clinical trial agreement (CTA) have been met and all outstanding payments to site have been made or requested.

3.4.2 :During Study Closeout :

1. Compile all of the required documents needed for the CRA to complete the closeout procedures.

2. Be available to respond to queries on the source data verification and CRF monitoring.

3. Communicate with the CRA to discuss items such as:

• Any outstanding issues or action items
• Requirements for participant follow-up, including post-study serious adverse events
• Procedures for handling of any data clarifications.
• Requirements for record retention and storage

4. Arrange for the return of all study-related materials, including the investigational product, or provide documentation of destruction, as authorized by the sponsor.

5. File copies of all investigational product shipping receipts and accountability records in the investigator study files

6. Organize all other study-related items for return such as CRFs, randomization code envelopes, and any loaned equipment.

7. Request information from the sponsor, such as:

• Anticipated timing to receive any outstanding payments
• Anticipated timing for availability of the final report
• Publication plans
• Feedback regarding site performance in the clinical research study
• Plans for inspections or audits

3.4.3 : Post Study Closeout :

1. Resolve any subsequent data queries that arise.

2. Confirm that the sponsor sends a written summary of key discussions and conclusions made during the study closeout. Follow up as necessary to obtain.

3. Obtain confirmation of return or destruction of all study-related materials such as equipment, unused laboratory supplies and CRFs and unused or returned investigational product, etc, and file records in the investigator study files

4. Distribute the clinical study report summary to appropriate personnel when available.

5. Check the investigator study files for completeness and prepare to archive the files according to local policies and sponsor agreement (usually only after the sponsor has confirmed that the database is closed).

3.4.4 : Communication regarding Study Closeout :

1. Inform all members of the clinical research team and all relevant departments (e.g., pharmacy, laboratory, diagnostic imaging) of the study closeout.

2. Inform the IEC about the completion of the clinical research study by submitting a final study report.

3. Provide a copy of the correspondence with the IEC to the sponsor.

4. Also arrangement to archive the documents for time frame required as per local regulations.(documents will be archived as per specifications in Clinical Trial Agreement)

5. Inform staff and participants as applicable about study results and publications once available.

3.4.5 : Special incidences in site closeout :

1. If the trial is prematurely terminated or suspended for any reason, the investigator/institution should:

Promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies).

2. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should:

Inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IEC.
Provide the sponsor and the IEC with a detailed written explanation of the termination or suspension.

3. If the sponsor terminates or suspends a trial, the investigator should:

Promptly inform the institution and IEC and also provide the detailed written explanation of the termination or suspension.

SOP NO. 04/04 :- SOP for Institutional Ethics Committee related activities.

4.1 : Preparing and Submitting documents for Initial and Expedite Institutional Ethics Committee (IEC) review :

4.2 : Safety Related Communication :

4.1 : Preparing and Submitting documents for Initial and Expedite Institutional Ethics Committee (IEC) review :

4.1.1 : Site to prepare Initial Review Documents for IEC submission :

The Site Team :

• Verify the completeness of the contents of the protocol submitted package to include the following documents:

- IEC Protocol submission form for initial review
- Submission letter
- Summary of protocol
- Amendments to protocol (if any)
- Investigator Brochure
- Informed consent document in English and Regional languages, which includes Marathi, Hindi, Gujrati (provided PI would know these languages completely) Back translations of Regional languages informed consent documents and back translation certificates.
- Amendments to the Informed consent document (if any)
- Case Record Form
- Subject recruitment procedures: advertisement, notices, etc.
- Patient instruction card, identity card, diary etc.
- Investigator's Undertaking , CV and registration certificate (registration certificate to be submitted whenever applicable)
- DCGI Approval if available.
- Regulatory permissions (as applicable)
- No Objection Certificate from Institution (NOC)

Protocol to include :-

1. Title of the Protocol
2. Name and contact details of Principal Investigator
3. Name and contact details of Sponsor
4. Abstract (summary/synopsis)
5. Type of Protocol (screening, survey, clinical trial and phase)
6. Objectives
7. Anticipated Outcome
8. Inclusion/Exclusion Criteria
9. Withdrawal or discontinuation Criteria
10. Schedule and Duration of Treatment
11. Modes of Treatment Studied
12. Methodology
13. Activity plan / Timeline
14. Efficacy or Evaluation Criteria (Response/Outcome)
15. Safety Parameters Criteria (Toxicity) .
16. Analysis (methods)

As per the requirement of IEC, site will submit three hard copies and one soft copy are required to be submitted for Institutional Ethics Committee records. Site would keep one copy for site record.

4.1.2: Protocol Amendments:-

- The Principal Investigator will submit required copies of Protocol amendment/protocol related documents
- Site will submit any amendments in study related documents for IEC review, with similar procedure which is followed for initial submission. All the relevant and necessary documents would be submitted

4.1.3 : Study report requirement of IEC :-

• The Principal Investigator is required to submit 1 copy of Periodic Study Report and related documents every 6 months.

• The Principal Investigator will submit 1 copy of Study Completion Report and related documents .

4.1.4 : Changes Requested by the IEC :-

1. If IEC requests changes to the study related documents, indicate the changes and forward to Contract Research Organization (CRO) and the sponsor for review.

2. Site to submit the revised study related documents (If provided by CRO or Sponsor)

3. Before implementing any new procedures or changes to study procedures resulting from any protocol amendments, the amendment and the revised ICF must be approved by the applicable regulatory agency(ies) and the IEC. The only exception to this would be in the situation of emergency use and general exceptions to informed consent (refer to the SOP on the informed consent process).

4. Obtain written and dated approval/favourable opinion from the IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements), and any other written information to be provided to subjects prior to the commencement of the trial. This is in the form of an IEC approval letter which should state the version number and dates of documentation submitted.

4.2 : Safety Related Communication :

4.2.1 : Defination of AE, SAE-Drug, SAE-Device, Unexpected adverse reaction :-

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) – drug

Any untoward medical occurrence that, at any dose:
a. results in death;

b. is life-threatening;
NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

c. requires in-patient hospitalisation or prolongation of existing hospitalisation;

d. results in persistent or significant disability/incapacity; or

e. is a congenital anomaly/birth defect; and fits the SAE criteria as specified in the relevant clinical trial protocol.

Serious Adverse Event (SAE) – device :

Serious Adverse Event for *medical devices*: any adverse medical occurrence that:
a. lead to a death;

b. lead to a serious deterioration in health of a patient user or other. This would include:

• A life threatening illness or injury

• A permanent impairment of body function or permanent damage to a body structure

• A condition requiring hospitalisation or increased length of existing hospitalisation

• A condition requiring unnecessary medical or surgical intervention e) foetal distress, foetal death or a congenital abnormality/birth defect

c. might have led to a death or a serious deterioration in health had suitable action or intervention not taken place.

This includes:

• A malfunction of a device such that it has to be modified or temporarily/permanently taken out of service

• A factor (deterioration in characteristics or performance) found on examination of the device.

Investigator and concerned personnels also need to refer definitions mentioned by regulators.

Unexpected adverse reaction:

• Nature or seriousness or severity or outcome when is not consistent with the applicable product information (Investigator's brochure or summary of product characteristics)

Regarding definitions mentioned above please also note , Investigator and concerned personnels also need to refer definitions mentioned by regulators.

4.2.2 : Determine Severity and causal Relationship :-

Study team should educate participants about expected adverse events and the importance of reporting it to the coordinator or investigator at clinic visits and/or during telephone contact.

At each clinic visit/telephone contact, document the details of any local AEs or SAEs. Grade the severity of the local AE using the protocol-defined criteria (i.e. mild, moderate or severe).

Assess and assign causality/attribution for any local AEs. The attribution or causality is the determination of whether an AE is related to the investigational treatment or procedure.

Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. The definitions may vary depending upon the sponsor, the study and the therapeutic area. Use the criteria indicated by the protocol.

If it is not defined in the protocol criteria mentioned in 4.2.2.1 and 4.2.2.2 can be used:

4.2.2.1 : Assessment of Intensity :-

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event which is incapacitating and prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the pre- defined outcomes as per "Definition of an SAE" mentioned in section 4.2.1.

4.2.2.2 : Assessment of Causal Relationship :-

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

Not Related In the Investigator's opinion, there is not a causal relationship between the study product and the adverse event.

Unlikely The temporal association between the adverse event and study product is such that the study product is not likely to have any reasonable association with the adverse event.

Possible	The adverse event could have been caused by the study subject's clinical state or the study product.
Probable	The adverse event follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study subject's clinical state.
Definitely	The adverse event follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

Note: The final assessment of the severity and causality of SAE must be made and signed-off by the PI or co-investigator or designated personnel.

4.2.3 : Report safety information to sponsor and IEC :-

Notify the Licensing Authority, the Sponsor or his representative and the Ethics Committee within 24 hours of their occurrence. The report of the serious adverse event of death and serious adverse event other than death, after due analysis shall be forwarded by the Investigator to Chairman of the Ethics committee and the chairman of the Expert committee constituted by the Licensing Authority with a copy of the report to the Licensing Authority and the head of the Institution where the trial has been conducted within fourteen calendar days of occurrence of the serious adverse event of death or other SAE.

For local SAEs, use the reporting methods provided by the sponsor to complete the required documentation for expedited reporting.
Examples of the types of information usually collected are as follows:
• Reporter information
• Protocol information
• Participant information (e.g., unique identifier, age/date of birth, gender, height, weight)
• Investigational product/treatment details (e.g., agent name, dose, frequency, route; dates)
• Description of event (e.g., diagnosis, presentation, clinical findings, results of diagnostic tests)
• Status/outcome (e.g., ongoing, fatal/death, recovered/resolved with sequelae, recovered/resolved without sequelae)
• Action taken (e.g., none, study treatment discontinued)
• Relevant laboratory data (if applicable)
• Concomitant medication(s)
• Other contributing cause(s), as applicable
• Adverse event name and grade using protocol-defined terminology and grading criteria
• Attribution/relationship to treatment or procedure
• Instructions for follow up information
• Other information required by the sponsor

"In case the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event."

4.2.4 : Record Keeping :-

1. If the local AE or SAE results in breaking the randomization code, document and inform the sponsor and the monitor as to why the code was broken. Also refer to the Section 7.6 .

2. Record all information about local AEs or SAEs in the Case Report Forms (CRFs) as required and ensure that all of this information is available in the source document. Follow up and report any ongoing local AEs or SAEs as required in the study protocol.

3. File copies of all communication with the sponsor regarding local AE or SAE reporting, including faxes, telephone calls, instructions given and follow up in the investigator study files.

4. Report all SAEs to the IEC according to IEC SOP.

5. Submit all safety reports/summaries (such as Investigational New Drug (IND) Safety Updates, Council for International Organizations of Medical Sciences (CIOMS) reports, MedWatch reports) and follow-up information on an ongoing basis to the IEC for acknowledgment or review, according to IEC requirements. Copies of the associated IEC correspondence should be provided to the sponsor, according to sponsor requirements.

6. The Qualified Study Team member must review safety reports received from the sponsor.

7. Submit safety reports/summaries and follow-up information to the IEC, according to IEC SOP.

8. File the safety reports and associated IEC correspondence in the investigator study files.

9. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IEC.

10 .Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

11. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented as AE.

12. For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

SOP NO. 05/04 :- SOP related to Informed Consent Form:

5.1 : Informed Consent Form (ICF) :-

1. The potential participant's consent must be freely obtained prior to any involvement in the study, and adequate documentation is required to verify that consent was obtained appropriately and prior to the initiation of any study-related procedures. However, informed consent is an interactive process that is ongoing throughout the participant's involvement in the study.

2. The PI/ designated person shall review the informed consent form and ensure that the patient information sheet is in accordance with schedule Y requirements.

3. The PI /designated person must ensure that the document has been customized with all the site details including the name of the PI, Name and address of the Institute, Contact details , Name of IEC representative , contact details of the IEC.

4. Freely given informed consent should be obtained from every participant prior to clinical research study involvement. Consent must be voluntary and without undo influence.

5. In obtaining and documenting informed consent, the investigator and coordinator should comply with all required guidelines.

6. Prior to the beginning of the involvement of human participants, the investigator must have documentation confirming the approval by the IEC.

7. As per new amendments in Schedule Y by DCGI office via Gazette Notifications, site should follow, (iv) An audio-video recording of the informed consent process of individual subject, including the procedure of providing information to the subject ad his understanding on such consent, shall be maintained by the investigator for record.",

5.2 : Obtaining Written Informed Consent :-

The written informed consent Form (ICF), which includes the Information sheet have documentation confirming the approval by the IEC and Consent Form, is an information tool used to conduct consent discussions with potential research study participants. The ICF also serves as an ongoing reference for study participants and provides written confirmation that informed consent was obtained.

The person obtaining informed consent should be qualified by training to do so, and documented on the task delegation form), should review the study details with the knowledgeable in the clinical research study and preferably the therapeutic area being studied. The investigator, or a qualified person designated by the investigator (as potential participant (preferably in a quiet and private location).

1. Before proceeding, confirm that the most recent version of the IEC-approved ICF is used.

2. Fully inform the potential participant of all pertinent aspects of the research study (i.e., all essential elements as described in the ICF), in non-technical language that is easy for the potential participant to understand.

3. Provide the potential participant with a copy of the ICF. The potential participant needs to read and comprehend the ICF before signing it. Allow the potential participant ample time to read the ICF and ask questions. This may include taking the ICF home to review with a family member or other trusted individual.

4. If the potential participant agrees to take part in the clinical research study, the participant must sign and date the Consent.

5. The person who conducted the informed consent discussion must also sign and personally date the ICF.

6. Obtain all required signatures prior to enrolling the participant into the research study or conducting any research-related procedures.

7. Provide the participant with a photocopy of the signed and dated ICF; the original will be retained at the site.

8. To enhance participant safety, participant's family physician be notified regarding involvement in a clinical research study. If the participant does not have a family physician or does not wish him or her to be notified of involvement in the study, document this accordingly.

9. The process of obtaining informed consent must be documented. In the event that the potential participant is not competent to consent to treatment, refer to section 5.4 and 5.5 of this SOP for instructions regarding the legally acceptable representative and the impartial witness.

5.3 : Ongoing Informed Consent : -

1. Inform the participant in a timely manner if new information becomes available that may be relevant to their willingness to continue to participate in the research study. Immediate notification of participants is necessary in cases of new information becoming available that indicate the potential for imminent danger with ongoing continued participation in the study.

2. Document the communication of this information in the participant's source documents.

3. Whenever important new information becomes available that may be relevant to the participant's consent, revised ICF and any other written information to be provided to study participants after IEC approval of such ICF.

4. During the participant's involvement in the research study, give the participant a photocopy of any signed and dated ICF updates, and a copy of any IEC approved amendments to any other written study information.

5.4 : Legally Acceptable Representative:-

1. If the potential participant is unable to provide informed consent, the investigator or a qualified person designated by the investigator should conduct the informed consent procedures with the participant's legally acceptable representative.

2. Inform the potential participant about the research study to the extent compatible with the potential participant's understanding and, if capable, get the potential participant to sign and personally date the written ICF.

3. Provide the participant or the participant's legally acceptable representative with a photocopy of the signed and dated ICF; the original will be retained at the site.

5.5 : Impartial Witness :-

1. If the potential participant or their legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other IEC approved information is read and explained, the potential participant or their legally acceptable representative must consent to be involved in the research study. Both the potential participant or legally acceptable representative (if capable) and the impartial witness must sign and date the ICF.

2. By signing the ICF, an impartial witness attests that the information in the ICF and any other IEC-approved written information were accurately explained to the participant or the participant's legally acceptable representative, and that informed consent was freely given by the participant or the legally acceptable representative.

5.6 : Documenting Informed Consent :-

Document the informed consent process in the source document, including:

1. Whether the potential participant was given ample opportunity to read the ICF and to decide whether or not to be involved in the research study.

2. Also document date and time of the consenting process. People involved in the consenting process. That the patient has provided the consent voluntarily.

3. Whether adequate time was given for all questions about the research study to be answered to the satisfaction of the potential participant. Response provided by PI/designated person to questions raised by patient should be documented.

4. Also there should be documentation that the subject can call the designated IEC person anytime for any clarifications.

5. Also document any other protocol specified information.

6. Document that informed consent was obtained prior to initiating any study-related Procedures. The participant was given a copy of the signed and dated ICF.

5.7 : Exceptions to the Informed Consent Requirements :-

Clinical research studies rarely include conditions where prior consent from a participant is not possible. Exceptions to the informed consent requirements are not covered in this SOP. Refer to the ICH Good Clinical Practice (GCP) Guidelines for information on obtaining consent in emergency situations.

5.8 : Audio/Video consenting :-

5.8.1 Informed Consent Form (ICF) :-

1. The potential participant's consent must be freely obtained prior to any involvement in the study, and adequate documentation is required to verify that consent was obtained appropriately and prior to the initiation of any study-related procedures. However, informed consent is an interactive process that is ongoing throughout the participant's involvement in the study.

2. The PI/ designated person shall review the informed consent form and ensure that the patient information sheet is in accordance with schedule Y requirements.

3. The PI /designated person must ensure that the document has been customized with all the site details including the name of the PI, Name and address of the Institute, Contact details, Name of IEC representative , contact details of the IEC.

4. Freely given informed consent should be obtained from every participant prior to clinical research study involvement. Consent must be voluntary and without undo influence.

5. In obtaining and documenting informed consent, the investigator and coordinator should comply with all required guidelines.

6. Prior to the beginning of the involvement of human participants, the investigator must have documentation confirming the approval by the IEC.

5.8.2 : Obtaining Written Informed Consent :-

The written informed consent Form (ICF), which includes the Information sheet have documentation confirming the approval by the IEC and Consent Form, is an information tool used to conduct consent discussions with potential research study participants. The ICF also serves as an ongoing reference for study participants and provides written confirmation that informed consent was obtained.

The person obtaining informed consent should be qualified by training to do so, and documented on the task delegation form, should review the study details with the knowledgeable in the clinical research study and preferably the therapeutic area being studied. The investigator, or a qualified person designated by the investigator should provide information to potential participant (preferably in a quiet and private location-consultation room).

1. Before proceeding, confirm that the most recent version of the IEC-approved ICF is used.

2. Fully inform the potential participant of all pertinent aspects of the research study (i.e., all essential elements as described in the ICF), in non-technical language that is easy for the potential participant to understand.

3. Provide the potential participant with a copy of the ICF. The potential participant needs to read and comprehend the ICF before signing it. Allow the potential participant ample time to read the ICF and ask questions. This may include taking the ICF home to review with a family member or other trusted individual.

5.8.3 Study where Audio-Video (A-V) Consenting is not required.

1. If the potential participant agrees to take part in the clinical research study, the participant must sign and date the Consent.

2. The person who conducted the informed consent discussion must also personally sign and date the ICF.

3. Obtain all required signatures prior to enrolling the participant into the research study or conducting any research-related procedures.

4. Provide the participant with a photocopy of the signed and dated ICF; the original will be retained at the site.

5. The process of obtaining informed consent must be documented. In the event that the potential participant is not competent to consent to treatment, refer to section 5.4 and 5.5 of this MRD SOP Version:1 for instructions regarding the legally acceptable representative and the impartial witness.

5.8.4 Study where Audio-Video Consenting is required.

At the beginning of the video recording process, the Investigator will identify the protocol, the subject/ Legally Acceptable Representative (LAR) / Impartial Witness (IW)and the language understood by the subject/LAR/IW. If the Investigator does not know the language of the subject/LAR/IW a member of the study team who understands the language, would become the interpreter.

The A-V recording should include the verbal confirmation by investigator and subject that subject has already given verbal consent 'Consent for Audio-Visual Recording of the Informed Consent Process'.

Audio-Visual Recording of the Informed Consent Process shall occur in quiet and well lilted room to ensure that the image is recognizable and the audio is clearly audible.

Investigator/Designee should introduce all the individuals participating the consent discussion and clearly identifying them by their names and role in the recording process.
While A-V recording following questions should be asked to the subject:

- Name of the subject
- Age/Date of Birth of the Subject
- Date, time and place where subject is video recorded

If potential patient is not competent to consent to treatment, refer to section 5.4 and 5.5 of this MRD SOP Version:1 for instructions regarding the legally acceptable representative and the impartial witness.

Following essential information would be provided to the potential participant:

1. Statement that the study involves research and explanation of the purpose of the research.

2. Expected duration of the Subject's participation.

3. Description of the procedures to be followed, including all invasive procedures.

4. Description of any reasonably foreseeable risks or discomforts to the Subject.

5. Description of any benefits to the subject or others reasonably expected from research. If no benefit is expected subject should be made aware of this.

6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.

7. Statement describing the extent to which confidentiality of records identifying the subject will be maintained and who will have access to subject's medical records.

8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)

9. Statement describing the financial compensation and medical management as under:
a. In the event of an injury occurring to the clinical trial subject, such subject shall be provided free medical management as long as required.

b. In the event of a trial related injury or death, the Sponsor or his representative, whosoever has obtained permission from the licensing Authority for conduct of the clinical trial, shall provide financial compensation for the injury or death.

10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury

11. The anticipated prorated payment, if any, to the Subject for participating in the trial

12. Subject's responsibilities on participation in the trial

13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled

14. Any other pertinent information

Additional elements, which may be required:

1. Statement of foreseeable circumstances under which the subject's participation may be terminated by the Investigator without the subject's consent.

2. Additional costs to the subject that may result from participation in the study.

3. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by subject.

4. Statement that the subject or subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the subject's willingness to continue participation will be provided.

5. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or foetus, if the subject is or may become pregnant), which are currently unforeseeable.

6. Approximate number of subjects enrolled in the study.

7. Privacy and Confidentiality.

Post A- V recording:

- Study personnel, having an obligation of confidentiality towards the patient should perform following activity post audio-video recording.
- Study personnel should check if the proceedings have been recorded completely before the subject is asked to leave from audio-video recording location.

- Study personnel should Check the quality of audio and video output

- Study personnel should download the file through the USB cable or media card directly into a study team computer and secure it by taking appropriate measures. One back-up copy shall be done on Central Computer in Medical Research Department. Both copies would be password protected and only study team members would have access to these recordings.

- Study personnel should also verify that the A-V file is deleted from recording device.

Documenting Informed Consent:-
Document the informed consent process in the source document, including but not limited to:

1. Whether the potential participant was given ample opportunity to read the ICF and to decide whether or not to be involved in the research study.

2. Also document date and time of the consenting process. People involved in the consenting process. That the patient has provided the consent voluntarily.

3. Whether adequate time was given for all questions about the research study to be answered to the satisfaction of the potential participant. Response provided by PI/designated person to questions raised by patient should be documented.

4. Also there should be documentation that the subject can call the designated IEC person anytime for any clarifications.

5. Also document any other protocol specified information.

6. Document that informed consent was obtained prior to initiating any study-related Procedures. The participant was given a copy of the signed and dated ICF.

5.8.5 Principle of privacy and confidentiality :

In order to maintain the confidentiality, one of the study team members would be engaged as videographer. Investigator should define and allocate the activities of audio-video recording of informed consent process to the respective identified person as videographer. The Investigator shall maintain the details of the person to whom he has delegated the duties of audio video recording.

5.8.6 Technical Requirements For A-V Recording, Transfer, Storage, Control & Archival

A. Hardware Modalities:
A-V recording device with facility for in-built storage of A-V files, USB port and USB cable and Tripod Stand.

Study team Computer would be used to store the audio-video recordings.

B. Transfer and storage on study team member computer and Central Computer:

Using USB cable of recording device/pen drive, transfer the recorded A-V files to 2 locations, study team member computer and Central Computer in Medical Research Department (As back-up) .

The A-V file would have a standardized nomenclature as mentioned below:
(E.g.: Protocol Number_Subject Number_and Date of Consenting.

After ensuring that the A-V files saved on the Central computer of Medical Research Department open and close properly, delete the files from recording device.

C. Archival:

- A-V files on study team member computer and Central Computer in Medical Research Department will be stored for 5 yrs.
- After 5 Years files will be deleted from both devices.

SOP NO. 06/04 :- SOP for Source Notes Writing and Data Management

6.1 : Source Document writing :-

Source documents, by definition, include all original documents, data, and records (eg. Hospital records, clinical and office charts , laboratory notes , subject diaries , or evaluation checklists , pharmacy dispensing records , recorded data from automated instruments, photographic negatives, microfilm or magnetic media , X-rays , subject files, and records kept at the pharmacy, or any other departments involved in clinical trials)

Site will review the protocol and the CRF to identify the critical data to be collected and may develop study-specific source documents, forms and checklists just to accurately collect the required data, if applicable.

Site will not use any standard printed source documents worksheets to document informed consent related procedure or study related procedure. Source documents worksheets would be used only if CRO or Sponsor has requested to note data on such source documents worksheets.

These Source documents worksheets would be used by the site only after IEC permission.
Source data would be recorded on hospital progress notes letterhead and should have following basic information on every page:

- Protocol No
- Patient Initial
- Patient No
- Date of visit
- Name and Sign of personnel writing the source notes

6.2 : Good Documentation practice and ALCOA principal :-

Site will follow ‘Good Documentation’ practice:

‘What is not documented is not done!’

‘Document what is done as well as what is not done!’

Roots of good documentation principles are in the ICH-GCP where source data and source document is first defined. Following are essential components of good documentation.

1. Attributable

It should be clear who has documented the data.

2. Legible

Readable and signatures identifiable.

3. Contemporaneous

The information should be documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.

4. Original

Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.

5. Accurate

Accurate, consistent and real representation of facts.

6.3 : Case Report Forms :-

1. Obtain information about the data collection process from the sponsor.

2. Review the protocol and the CRF to identify the critical data to be collected and develop study-specific source documents, forms and checklists to accurately collect the required data, if applicable.

3. Maintain a list of responsible staff that have been delegated the task of CRF completion by the Principal Investigator.

6.4 : Completion of Case Report Forms (CRF's) :-

The sponsor when applicable should provide guidance to investigators on completing CRFs and making CRF corrections. However, the following general procedures apply:

1. Complete CRFs in timely manner as possible.

2. The principal investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and in all required reports. This should be indicated by the PI signature.

3. Transcribe the required data accurately from the source documents. The data recorded in the CRF should be consistent with the source documents or the discrepancies should be explained.

4. Complete all data fields according to the sponsor requirements.

5. If an error is made in the CRF:
• Cross out the original incorrect information with a single straight line.
• Do not obscure the original incorrect entry.
• Do not erase an original incorrect entry.
• Do not use correction fluid (white out).
• Place the correct information next to the original incorrect entry.
• The person making the changes should initial and date all corrections.
• Reason for change be indicated if not obvious.

6. Follow sponsor's instructions for compliance with applicable regulations for electronic data collection and transfer.

6.5 : Case Report Form Review: Data Verification :

At monitoring visits (if applicable), the sponsor's monitor will confirm that the CRFs are accurate, legible, complete and verifiable from the source documents.
1. In preparation for monitoring, Site to ensure that the CRFs that will be monitored should be available for review, along with the corresponding source documents.

2. Ensure that all data queries to date have been resolved to the extent possible.

3. Arrange for the PI to review and sign any completed CRFs as required.

4. The monitor will conduct a review of the completed CRFs .

5. Review any noted discrepancies in the data with the monitor.

6. Any change or correction to a CRF should not obscure the original entry.

7. The monitor may retrieve any completed and signed CRFs for entry into the sponsor's database for eventual analysis. Copies should be retained at the site.

6.6 : Case Report Form Review: Data Clarification and Resolution :

Once the CRFs are completed, the data are usually entered into a study-specific database.
Built-in data checks are normally conducted and discrepancies are flagged. Data discrepancies (e.g., Date of Birth wrongly mentioned) may generate data clarification forms (DCFs) that will be sent to the site for resolution.

All data that are conflicting, ambiguous or illegible will also result in a data query.

1. Once completed CRF pages have been submitted to the sponsor, Site will not make any changes to the investigator site copy. Site will follow the sponsor's directions for further corrections.

2. Make corrections to the DCF (or equivalent) using the same procedures as for the CRFs. This form becomes an extension of the CRF.

3. Only make corrections that can be validated by the source documents.

4. Do not change data at the request of a monitor if there is disagreement. Discuss these discrepancies with the Principal Investigator or authorized designate for final resolution.

5. Have the PI or authorized designate review and sign all DCFs, as required.

6. A legible copy should be stored with the CRFs.

6.7 : Record Retention and Archiving :-

1. After final study closeout, all of the essential clinical research study documents (e.g., investigational product accountability logs, CRFs, data clarification forms, lab manuals, investigator meeting records) should be compiled and checked for completeness.

2. Take measures to prevent accidental or premature destruction of the essential documents (e.g., clearly identify storage boxes; keep records of stored items and retention dates; store in locked area).

3. Prepare to archive the files (e.g., place in long-term on-site or off-site storage) according to CLINICAL TRIAL AGREEMENTS SPECIFICATIONS only after the sponsor agreement (usually only after the sponsor has confirmed that the database is closed).

4. At the request of the sponsor, auditor, IEC or regulatory authorities direct access to all clinical research-related records must be made available.

5. Studies records would be retained according to applicable regulations, contract or for years whichever is longer.

SOP NO. 07/04 :- SOP related to Investigational Product :

7.1 : Receipt and Inventory of Investigational Product(s) :-

Upon receipt of the investigational product at the site, PI designated personnel should conduct the following activities:

1. Inventory: confirm that the information on the packing record matches what has been shipped to the site (i.e., number of packages, quantity per package, size (if device), lot or batch numbers). Complete and return the form acknowledging receipt (if required by the sponsor), and file a copy of the form and courier airway bill(s) in the study files (if required by the sponsor) .

2. Packaging: check that the investigational product has been packaged to prevent breakage, contamination and unacceptable deterioration during transport and storage.

3. Records: Document the receipt date, quantity and lot numbers of all investigational product(s) received from the sponsor in the investigational product accountability record/log.

4. If IP is received outside temperature range or is hampered the IP shall be quarantined and the sponsor representative shall be informed as soon as possible. All the above process , discussion, comments etc shall be documented appropriately.

5. Remove and secure blinding envelope, if provided.

7.2 : Storing the Investigational Product(s) :-

1. Written information for handling the investigational product(s) should be received from the sponsor, including: storage temperature(s) and acceptable range(s) storage conditions (e.g. protection from light) storage duration (e.g., expiry dates, re-test dates)

2. PI or designated personnel as per the delegation log, shall handle the IP all throughout the duration of the study.

3. PI designated personnel will keep record of storage temperatures as required. Record should also clearly mention the site specific holidays.

4. Any deviation from the recommended storage conditions should be documented on the temperature log along with the comments mentioning the reason for such deviation and such deviations would be immediately reported to site monitor and sponsor.

5. Temperature will be measured with a calibrated temperature monitoring device.

6. Store the investigational product(s) in a secure environment (e.g., room with locks) to restrict access to qualified and authorized personnel only. Confirm that doors to the storage units can be locked as required.

7. When equipment (where IP or study related material is stored) is not maintaining desired temp, IP should be immediately transferred to another calibrated equipment and same to be notified to site monitor. It should also to be notified to Sponsor if specified by the sponsor.

7.3 : Preparation of the Investigational Product :-

1. When required, IP need to reconstitute at site as instructed in the protocol.

2. PI should identify qualified personnel to reconstitute the IP.

3. When separate unblinded personnel is required to constitute the IP, it should be reconstituted in a separate place where confidentiality is maintained.

4. IP will be reconstituted and handed over to the designated personnel who would be administering the IP. It would be handed over within time as instructed in the protocol.

5. Transportation of IP from reconstitutation room to injecting room will be done in desired temp and as instructed in the protocol

7.4 : Dispensing the Investigational Product :-

1. Before dispensing the investigational product, confirm that appropriate storage conditions are maintained

2. The investigational product must be used only in accordance with the approved protocol.

3. Complete the investigational product accountability or dispensing record each time the investigational product is dispensed.

4. Provide each participant with the instructions on the proper use, handling, storage, and return of the investigational product(s). Document this discussion in the source documents.

5. Assess participant compliance with the instructions at intervals appropriate for the research study as specified within the protocol.

7.5 : Randomization Procedure :-

Follow the randomization procedures as described in the protocol. Retain all documents relating to randomization by external sources, such as an Interactive Voice Response System (IVRS).

7.6 : Unblinding Procedure :-

1. For blinded trials, confirm that the coding system for the investigational product(s) includes a mechanism that permits rapid identification of the product(s) in case of a medical emergency.

2. Follow the protocol-specific requirements for unblinding the investigational product. Promptly document and explain to the sponsor any premature unblinding of the investigational product(s) such as, accidental unblinding or unblinding due to a serious adverse event, same also need to be notified to IEC.

7.7 : Return or Destruction of Investigational Product :-

1. At the conclusion of the study, or as participants complete the research study, all documentation regarding receipt, storage, dispensing and return/destruction (if applicable) of investigational product must be complete and accurate and stored in the study files.

2. Designated personnel will review the accountability records and conduct a final inventory and reconciliation and prepare for return shipment to the sponsor.

3. The sponsor must provide written authorization for destruction of investigational product at the study site.

4. If the product is to be destroyed at the site, the site must have the appropriate procedures, permits and policies to do so. A copy of the destruction policy should be available and a copy filed in the investigator study file.

5. Provide the sponsor with documentation of destruction and copy to files. Return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirements).

SOP NO. 08/04 :- SOP for Participant care and related activities

8.1 : Patient Recruitment :-

1. Identify potential recruitment methods or strategies related to each area of the recruitment process. Obtain IEC approval of recruitment methods and materials.

2. PI should start pre-screening patients as soon as required approvals are obtained so that recruitment can be started as soon as site initiation visit is done.

3. Patient will be pre-screened from hospital data base (if maintained by PI) or referred patients. As per hospital policy there is no record maintained for out patient department patients. Record is maintained in medical record department only for inpatient department.

4. PI to motivate staff to maintain an acceptable level of recruitment effort for the duration of the study (e.g. provide training or information sessions about study protocol).

5. Modify the recruitment plan/strategy as necessary.

8.2 : Patient Registration for Clinical Drug Trial :-

1. PI or designated personnel will make sure that participant also gets registered for all visits (visits as mentioned in the protocol) as per the registration procedure of the institute.

2. Study team would instruct participants to get registered with hospital registration system for all hospital visits.

3. Participant registration doesn't mean PI has examined the participant but only informs that participant has visited the hospital.

8.3 : Participant Care before start of the study :-

1. PI or designated person will examine and investigate participant to conclude the diagnosis of the patient and also shall ensure consistency in the documentation across all relevant subject records.

2. If the participant has any general practitioner, he or she shall be informed regarding the subject's participation in the trial (If patient permits to do so). This discussion with the general practitioner shall be documented.

3. PI or designated person would note down thorough past and present medical history on hospital progress record sheets. All medications including their dose, route etc. will be recorded.

4. All the participants previous medical records will be collected, photocopied and maintained in subject's source records. All photocopy medical records should be authenticated by PI or designated person by signing and dating.

5. Participant will be given contact details for all study team, also contact details and correspondence address will be obtained from the participant.

8.4 : Participant care during the course of the study :-

1. The study co-ordinator shall call the subject and schedule the visit in accordance with the protocol. This should be documented in the source notes.

2. Principal Investigator and qualified designated person should do the clinical examination on regular intervals irrespective of the protocol specified procedures.

3. Study co-ordinator would interview patient regarding AE for all visits and same to be documented in source notes.

4. All the study procedures to be performed as per the protocol.

5. The participant's travel expense shall be reimbursed in total.

8.5 : Participant care at the end of the study :-

1. All the follow-up procedures to be performed as specified in the protocol.

2. PI or designated person shall inform general practitioner of the participant regarding the end of the trial.

3. The participant shall be followed up for atleast one month post the final visit , irrespective of the timelines specified in the protocol. Details of these visits shall be documented in source notes.

8.6 : Lost To Follow-up :-

1. If participant doesn't turn up for a scheduled visit the site shall make all the efforts (at least 7 unsuccessful telephone contacts and 1 written correspondence) to contact the participant before considering the participant as lost to follow-up. All these efforts to contact the participant shall be documented in the source notes.

2. For screen failure participants the PI shall ensure the regular standard of care as per the hospital guidelines.

SOP NO. 09/04 :- Lab Related

9.1 : Biological Sample Management :-

1. Obtain all of the sample management details from the sponsor or central laboratory if not described in the protocol, including:

• Laboratory contact information (for central laboratories)
• Requirements for specimen collection, labeling, processing and storage
• Supplies
• Packaging and shipping specifications.

2. The sponsor should provide detailed instructions for sample management prior to study activation. All supplies should be available prior to study activation.

3. Site to check equipment such as centrifuges, storage refrigerators/freezers and thermometer for their calibration and should be checked on a regular basis.

9.2 : Collecting Biological Samples :-

1. Ensure that proper informed consent has been obtained from the study participants, as part of the study specific informed consent process, prior to specimen collection.

2. Obtain and prepare the necessary equipment and supplies for sample collection (e.g., collection containers/tubes, labels, needles, vacutainers), paying close attention to collection tube colour, type and expiry date.

3. Add the appropriate labels to the collection containers (preferably pre-printed, participant-specific and bar-coded, if available).

4. Prepare any required laboratory requisitions.

5. Use protective equipment as required and collect samples according to the protocol instructions and using universal precautions.

6. For time-sensitive samples (e.g., pharmacokinetic studies), the same clock or watch must be used to record the precise drug administration and sample collection times.
If another staff member will be collecting any of the time-sensitive samples, use the same clock or synchronize study team watches.

7. Record the date and collection time in the participant's source document (e.g., pharmacokinetic worksheet) and on the laboratory requisition label as required.

8. Prepare samples for immediate processing as instructed in the protocol (e.g., invert, place on ice, refrigerate, freeze, transfer to centrifuge, transfer to laboratory for analysis).

9.3 : Processing and Storing Biological Samples :-

1. For those samples not sent immediately to the laboratory for analysis (e.g., pharmacokinetic or pharmacodynamic samples), prepare the necessary equipment and supplies for sample processing (e.g., centrifuge, storage containers, pipettes, labels).

2. Ensure that the appropriate specimen handling area is used

3. Label the storage containers.

4. Process the sample according to the protocol instructions (e.g., centrifuge speed, duration and temperature).

5. For centrifuged samples, harvest the required specimen and transfer to the appropriate storage container.

6. Dispose of unused specimens, or specimen waste, using proper disposal procedures.

7. Record any additional required information not already pre-printed on the label.

8. Store the sample in a dedicated area under the required storage conditions (e.g., light sensitivity) and temperatures (e.g., room temperature, refrigerate, freeze).

9. Refrigerator and freezer temperatures should be monitored using calibrated devices and recorded on a regular basis to ensure the temperatures remain within the range allowed in the protocol.

10. Temperature-controlled storage units (refrigerators, freezers) would be configured to alarm if malfunctioning or during power failures so that samples remain viable. Site will make sure uninterrupted power supply (back-up power) be available for refrigerators or freezers used for storage of biological samples.

9.4 : Handling Biological Samples in Preparation for Shipping :-

1. Confirm the appropriate method of transportation of samples from the site to the laboratory with the sponsor (e.g., courier, internal manual collection schedule).

2. Determine if any special forms, permits or custom processes are required for shipment of the samples.

3. Determine the proper timing for sample shipments (e.g., in batches of specific numbers, after each individual collection) and the anticipated turnaround time for results, if applicable.

4. Review the sample packaging requirements and package the sample(s) as indicated in the protocol or central laboratory manual. The sponsor should supply a checklist with specific packaging and transportation instructions, which should include the following information:

• How the samples should be packaged for transport

• How the samples should be contained

• How the samples should be labeled

• Instructions for transportation of the samples

• Instructions for storage conditions of the samples including temperature and stability requirements (e.g., do not shake)

• Shipping documents and how to complete correct information

• Proper labeling of the samples (e.g., type of class)

• Proper safety mark for the samples (e.g., labels, letters)

• Number of quantities that can be shipped at one time

• Contact numbers and names of personnel to be notified of transport

5. If dry ice is needed, review the proper technique for handling dry ice.

6. Complete the appropriate documentation (e.g., sample shipping log).

7. Maintain the required storage temperature while waiting for pick-up.

8. Retain a copy of the shipping receipt (or courier waybill) and commercial invoice (if applicable) and file in the investigator study files with copies to the sponsor as required.

9. For air shipping samples if Sponsor or CRO need personnel, who is certified by International Air Transportation Agency (IATA) then training to be arranged by CRO or sponsor.

9.5 : Training :-

Personnel responsible for biological sample management should:

1. When possible, attend the investigator meeting to obtain protocol-specific details for biological sample management.

2. Be aware of the laboratory safety procedures available at the site.

9.6 : Equipments :-

1. Temperature-controlled storage units (refrigerators, freezers) would be configured to alarm if malfunctioning or during power failures so that material remains viable. Site will make sure uninterrupted power supply (back-up power) be available for refrigerators or freezers used for storage of study related material.

2. All equipments intended to be used for clinical trials must be calibrated and calibration certificate must be maintained in Investigator Site File.

3. Site personnel to follow-up a one month before the expiry of calibration to get extended or new calibration certificate.

SOP NO. 10/04 :- Inspection and Audits

10.1 : Inspection or Audit Planning :-

1. Sponsor or CRO may notify regarding audit/inspection to the site. If notification is from the regulatory authorities directly, site need to notify it to the sponsor and CRO.

2. Verify the following with the sponsor, as appropriate (i.e., if not covered in notification letter):

• Purpose of the audit/inspection
• Audit/inspection plan and procedures
• Audit/inspection reporting: documented observations and findings of the auditor(s)

• Follow-up requirements

3. Confirm the agreed date(s) and time of the audit/inspection and exit interview with the sponsor and/or regulatory agency.

4. Notify all relevant staff members of the audit/inspection (e.g., PI, co-investigators, clinical research coordinator(s), pharmacy, laboratory, technical departments).

5. Review audit/inspection procedures with study personnel and conduct a thorough review of the study procedures, study protocol, case report forms (CRFs), source data and study documentation.

10.2 : Preparing for an Inspection or Audit :-

1. Site will identify a suitable work area for the auditor(s)/inspector(s). Area must be quiet and free of other study records or other files.

2. Assemble the requested documentation as applicable, such as:

- Case report forms (CRFs)
- Data clarification forms (DCFs)
- Informed consent documents (ICDs)
- Source documents
- Study files, including:

• Signed protocol and protocol amendments
• Ethics approval letters and other ethics documentation
• Current investigator brochure
• Up-to-date list of study personnel including CVs
• Completed and signed regulatory forms

• Sponsor correspondence
• Laboratory documents including reference ranges and accreditation
• Investigational product accountability records
• Study logs (e.g., participant recruitment log, task delegation log)
• Equipment calibration and maintenance records (e.g., freezer/refrigerator temperature logs)
• List of SOPs
• Other items as requested

3. Site will take all efforts so that all required personnel are available on the day of the audit or inspection.

4. Check that participant recruitment records are current and complete.

5. Confirm with the appropriate staff members that all investigational product is accounted for and records are current.

6. Review CRFs, DCFs, and the investigator study files for content, completeness and accuracy. Check that all data are legible. Ensure that all corrections have been signed and dated. All essential documents should be properly filed.

7. Document and resolve any discrepancies.

8. Appoint a site delegate to act as contact for the auditor(s)/inspector(s).

10.3 : During the Inspection or Audit :-

1. Meet with the inspector/auditor as scheduled. Sponsor representative(s) may also be present.

2. Verify the credentials of the auditor/inspector

3. Record the name, contact information and title of the auditor/inspector.

4. Participate in the pre-inspection interview, if requested. Topics for discussion may include:

• Regulations and GCP guidelines
• Protocol review
• Recruitment process
• Informed consent process
• IEC processes
• Delegation of study tasks

5. Accompany the auditor/inspector on a tour of the work area, if previously arranged. Auditors/inspectors should be accompanied at all times by site staff. Areas visited may include:
• Clinical areas and examination rooms
• Laboratories
• Pharmacy
• Work areas for the study staff
• Storage areas for study drug and other study supplies

6. Provide the audit/inspection package and all documents requested by the auditor(s)/ inspector(s), including access to the study records and files.

7. Ensure that questions are answered by the most appropriate personnel. If asked questions by the auditor(s)/ inspector(s), instruct staff to describe their area of responsibility, to seek clarification if they do not fully understand any questions, not to answer any questions if they are not qualified to give a proper answer.

8. Provide photocopies of study-related documents requested by the auditor(s)/ inspector(s) (in accordance with institutional privacy policies). Record the list of documents requested by the auditor(s)/ inspector(s).

9. Ensure that the required personnel are present at the exit interview: Principal Investigator, designated research staff, and other personnel and/or sponsor representatives, as required.

10. Record the observations given by the auditor(s)/ inspector(s), and any discussion.

10.4 :Inspection/Audit Follow-Up :-

1. The auditor or the sponsor may communicate inspection observations and/or audit findings to the site. Follow up with the sponsor or the inspector/auditor to obtain an inspection or audit report, if possible.

2. Review the audit/inspection report with the appropriate staff (including the principal investigator), and the sponsor representatives.

3. Prepare written audit/inspection response and reply to each item/observation in the report. Include clarification or corrective action that will be taken. Forward the response to the sponsor/regulatory agency by the requested date, as applicable.

4. Perform corrective actions as described in the audit/inspection response.

5. File audit/inspection documents in the appropriate confidential investigator study files at the site.

MRD SOP NO. 11/04 :- Guidelines for Investigator Initiated Research study (IIRS) STUDIES

Investigator is the person responsible to the sponsor (if different from himself or herself) and applicable regulatory authorities for the conduct of the research study proposed . (eg. Clinician, Dentist Phd, pharmacist, physiotherapist).

In these cases, the IEC individually assesses the suitability of the **Investigator's** credentials for the type of study being proposed.

If there is no other organization playing role of Sponsor, Investigator would be considered as sponsor.

Note: All Site SOP's are applicable to IIRS following are specific guidelines. Also note that following guidelines are required for studies that involve studying new drug, device or procedure and all the aspects may not be applicable for observational studies and so Investigators are requested to seek guidance as required for their studies.

Following is sample cover for designing a protocol

CONFIDENTIAL
PROTOCOL TITLE
Protocol No: ----------
Version: ---------Date: ---------

SPONSOR

ADDRESS ----------
Phone: ----------

PRINCIPAL CLINICAL INVESTIGATOR
PRINCIPAL INVESTIGATOR NAME ADDRESS

Phone: ----------

AMENDMENTS:

1.	2.	3.	4.

AUTHORS
NAME
AND ADDRESS OF AUTHOR

STUDY CENTRE
NAME, ADDRESS
AND TELEPHONE NUMBER OF STUDY CENTRE

BIOSTATISTICIAN
NAME AND
ADDRESS OF STATISTICIAN (IF APPLICABLE)

STUDY MONITOR
NAME AND ADDRESS OF STUDY MONITOR

SPONSOR'S MEDICAL REPRESENTATIVE NAME
AND ADDRESS OF
SPONSOR'S MEDICAL EXPERT (if different from investigator)

STUDY
ACKNOWLEDGMENT/CONFIDENTIALITY

By signing this Protocol, the Investigator(s) acknowledges and agrees:
The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice[1] (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the drug relating to pre-clinical and prior clinical experience, which was furnished by the Sponsor, will be made available to all physicians, nurses and other personnel who participate in the conducting of this study. The Investigator will discuss this material with them to assure that they are fully informed regarding the drug(s) and the conduct of the study.

This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing by sponsor or such disclosure is required by any laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.
Sponsor will have access to any source documents from which Case Report Form information may have been generated. The Case Report Forms and other data pertinent to this study are the sole property as specified in clinical trail agreement .

The conduct and results of this study will be kept confidential. The results of this study may be published. Upon completion of the Study it is the intention of the parties to prepare a joint publication regarding or describing the Study and all the results there from and both parties shall co-operate in this regard.

Investigator Signatory:

PRINCIPAL INVESTIGATOR – NAME AND TITLE

Signature:

Date

Sponsor Signatory:

SPONSOR SIGNATORY – NAME AND TITLE
Signature: Date

Table of Contents

1 Synopsis

Study Title:
Protocol Number:
Development Phase:
Indication:
Study Drugs: (Including test, comparator, dosage form, dosing regimen and route)

No. Subjects:
No. Centres:
Study Duration:
Objectives of the Study:

Study Endpoints: (Primary and Secondary)
Study Design: Eligibility Criteria (Inclusion and Exclusion)

Study Procedures: (Including pharmacokinetic (PK) sampling times)

Safety Parameters/analysis:

Laboratory Parameters/Analysis: Total Blood Volume:
Sample Size Determination: (If applicable)

Statistical Analyses: (Brief Description)

Others :
(As required by the specific study)

2 Introduction

The introduction should outline all the background information and provide a justification for conducting the study in a logical, well ordered fashion. This should include: An overview of the target indication and population for the product; A summary of pre-clinical and clinical data that is relevant to the trial, including data that justifies the use of the study medication in the target indication, with literature references; A summary of the known and potential risks and benefits, if any, to human subjects; And a description of, and justification for, the route of administration, dosage, dosage regimen and treatment period(s).

3 Objectives

A detailed description of the objects of the study should be provided, split in to primary and secondary objectives as appropriate.

4 Study Design

An overview of the study design should be provided. A description of the type/design of the study should be given (i.e. double-blind, placebo-controlled, parallel design e.t.c.), with a description of the population to be studied, trial treatments, periods and expected duration of each period. A specific statement of the primary and secondary endpoints should be given, and a description of measures taken to avoid bias (i.e. randomisation, blinding etc).

5 Study Population

A full description of the study population should be given, including age, sex, condition .

5.1 Number of subjects

The total number of subjects should be provided, along with the number of subjects per specific study cohort if appropriate.

5.2 Inclusion Criteria

All subject inclusion criteria should be listed. Criteria should be specific and unambiguous and outline a population suitable for the phase of the study.

5.3 Exclusion Criteria

All subject exclusion criteria should be listed. Criteria should be specific and unambiguous and should take in to account any cautions and contraindications for the investigational compound(s) and study procedures.

5.4 Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the Investigators' Brochure (IB) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study.

6 Study Assessments and Procedures

All study assessments and procedures should be outlined in a clear, logical and unambiguous fashion. The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design, and interpretation of the design within the protocol. It is therefore extremely important that the protocol specifically outlines each study procedure in sufficient detail for all procedures to be performed in an identical fashion.

Procedures should be described for each phase of the study

6.1 Screening Evaluation

6.2 Study Procedures

6.3 Efficacy Assessments

All efficacy assessments and procedures should be outlined in detail, or referenced to a separate document or the appendices. Copies of assessment questionnaires should be appended to the protocol.

6.4 Study Restrictions

All study restrictions should be outlined in the section below, together with the duration and period of the study to which the restrictions apply.

6.5 Safety Assessments

Procedures for all safety assessments should be detailed, or a reference provided for the procedure (e.g. a laboratory handbook etc).

6.6 Pharmacokinetic Sampling

6.7 Pharmacodynamic Sampling

7 Investigational product(s)

7.1 Description of Investigational Product(s)

A description of all investigational products should given (including rescue medication), including dose(s), dosage regimen(s), dosage form(s), excipients and origin.

7.2 Dose Justification

A justification for the dose of investigational product(s) should be provided, with associated literature references as appropriate.

7.3 Comparator Justification

A justification for the comparator used in the study should be provided if appropriate, with associated literature references.

7.4 Administration

Specific details on the administration of each investigational product should be provided, with any precautions if appropriate.

7.5 Randomisation

7.6 Unblinding

7.7 Product Labelling

7.8 Handling and Storage of Study Drugs

All accountability procedures for the investigational drug, including placebo and comparators should be provided, with specific storage instructions.

8 Adverse Events (AE) and Serious Adverse Events (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol

8.1 Definition of an Adverse Event (AE)

Refer section 4.2.1 (MRD SOP)

8.2 Definition of a Serious Adverse Event (SAE)

Refer section 4.2.1 (MRD SOP)

8.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. ECG, vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, SAE Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a disease reported in the medical history, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.4 Time Period, Frequency, and Method of Detecting AEs and SAEs

All adverse events will be recorded between the time of consent and the follow-up visit. Each subject will be monitored regularly by the investigator and study personnel for adverse events occurring throughout the study. Patient should be interviewed on all hospital visits for any AE and whenever required. Same need to be documented in source notes.

8.5 Recording of AEs and SAEs

1. When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in to the CRF.

2. For each adverse event, start and stop dates, action taken, outcome, intensity (see Section 4.2.2) and relationship to study product (causality) (see Section 4.2.2) must be documented. If an AE changes in frequency or intensity during a study, a new entry of the event must be made in the CRF.

3. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented.

4. All details of any treatments initiated due to the adverse event should be recorded in the subject's notes and the CRF.

8.6 Prompt Reporting of SAEs to Sponsor

1. Once an investigator becomes aware that an SAE has occurred in a study subject, he/she will immediately notify the sponsor by contacting the study monitor via telephone to notify him/her of the event. The SAE form must be completed as thoroughly as possible with all available details of the event, signed by the Investigator.

2. Investigator (or appropriately qualified designee) should fax or email to the study monitor within 24 hours of first becoming aware of the event.

3. If the investigator does not have all information regarding an SAE, ***he/she will not wait to receive additional information before notifying the study monitor*** of the event and completing the form. The form will be updated when additional information is received.

4. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 4.2.2, "Assessment of Causality". If data obtained after reporting indicates that the assessment of causality is incorrect, then the SAE form may be appropriately amended, signed and dated, and resubmitted to the Sponsor.

5. In accordance with local IEC requirements, the investigator must also notify their Ethics Committee of any SAEs according the guidelines of the Ethics Committee.

6. The investigator, and others responsible for subject care, should institute any supplementary investigations of serious adverse events based on their clinical judgement of the likely causative factors. This may include seeking further opinion from a specialist in the field of the adverse event. Sponsor may also request extra tests. If a subject dies, any post-mortem findings, including histopathology will be provided to the sponsor (if available). No medical help, diagnosis, or advice should be withheld from the subject due to an inability to contact sponsor.

8.7 Expeditable Events

Expeditable events are those adverse events that are **CAUSALLY** related to the study product, **AND** that are both **SERIOUS** (see Section 4.2.1) and **UNEXPECTED** (see Section 4.2.1). Such events are subject to expedited reporting to regulatory authorities and will be reported within the stipulated timelines by Sponsor or a suitably qualified designee.

8.8 Evaluating AEs and SAEs

8.8.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event which is incapacitating and prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the pre- defined outcomes as per "Definition of an SAE" which is mentioned in Ethics Committee related SOP section.

8.8.2 Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the IB and/or product information in the determination of his/her assessment.

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

Not Related In the Investigator's opinion, there is not a causal relationship between the study product and the adverse event.

Unlikely The temporal association between the adverse event and study product is such that the study product is not likely to have any reasonable association with the adverse event.

Possible The adverse event could have been caused by the study subject's clinical state or the study product.

Probable The adverse event follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study subject's clinical state.

Definitely The adverse event follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

8.8.3 Assessment of Expectedness

Expected An adverse reaction, the nature or severity of which is consistent with the applicable product information (e.g. Investigators' Brochure) for an unapproved medicinal product).

Unexpected An adverse reaction, the nature or severity of which is not consistent with information in the relevant source document (e.g. Investigators' Brochure for an unapproved medicinal product).

8.9 Follow-up of AEs and SAEs

1. After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to Sponsor on the subject's condition.

2. All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

3. All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

4. New or updated information will be recorded on the originally completed SAE form, with all changes signed and dated by the investigator. The updated SAE form should be resent to Company Name.

8.10 Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside the AE/SAE detection period as defined in the protocol. Investigators are not obligated to actively seek AEs or SAEs in study participants in outside detection period. However, if the investigator learns of any SAE, including death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify Sponsor.

9 Subject Completion and Discontinuation.

9.1 Subject Completion

The definition of a completed subject should be provided.

9.2 Stopping Rules / Discontinuation Criteria

The details and justification of any stopping rules or discontinuation criteria should be provided.

9.3 Subject Withdrawal

Subject withdrawal criteria should be provided, and withdrawal procedures outlined. This should include: When and how to withdraw subjects; the type and timing of data to be collected; whether and how subjects are to be replaced; the follow up process for withdrawn subjects.

9.4 Early Termination of the Study

The study may be terminated prematurely by the principal investigator or his/her designee and the sponsor if:

- The number and/or severity of adverse events justify discontinuation of the study
- New data become available which raise concern about the safety of the study drug, so that continuation might cause unacceptable risks to subjects.

In addition Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must contact all participating subjects within two weeks, and written notification must be sent to the Ethics Committee.

10 Case Report Form (CRF)

A Case Report Form (CRF) will be completed for each study subject summarising all clinical screening and study data. Subjects will only be referred to in the CRF by their subject number and initials in order to retain subject confidentiality.
The completed original CRF's are to be sent to the Sponsor as soon as practical after completion and review. A copy of each completed CRF is to be retained by the Investigator for a period of time as determined by local regulations.

11 Data Analysis and Statistical Considerations

11.1 Hypotheses

If applicable.

11.2 Endpoints

Details of all efficacy/safety endpoints should be provided as applicable. If appropriate, these should be split in to primary and secondary.

11.3 Sample Size

The following should be considered and included in this section: Number of subjects planned to be enrolled - in multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified; The reason for choice of samples size, including reflections on (or calculations of) the power of the trial and level of significance with clinical justification; And the selection of subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, evaluable subjects etc).

11.4 Statistical Analysis

A description of all statistical methods to be employed, including timing of any planned interim analysis(ses) should be outlined. Procedures for accounting for missing, unused, and spurious data and reporting any deviation(s) from the original statistical plan should be described and justified.

11.5 Additional Analysis

Any additional analysis should be outlined as appropriate.

12 Data Management

An outline of the data management process should be outlined, to include: Where the analysis will take place; how data will be entered on the database; how data will be tracked, checked and audited; And which SOPs are to be followed.

13 Monitoring and Quality Assurance

1. The task of the Study Monitor is to guarantee the best conduct of the study through frequent contacts by phone and in person with the responsible Investigator, in accordance with the Monitor's Standard Operating Procedures, with the purpose of facilitating the work and fulfilling the objectives of the study. These site visits will enable the Monitor to maintain current, personal knowledge of the study through review of the records, comparison with source documents, and observation and discussion of the conduct of the study with the Investigator. The Monitor is responsible for monitoring adherence to the Protocol and completion of the CRF, and for the relationship between the Investigator and Sponsor.

2. The organisation, monitoring, supply of study materials and quality assurance of the present clinical study is the responsibility of Sponsor or its designee.

3. In order to ensure the accuracy of data, direct access to source documents by the representatives of both the Study Monitor and regulatory authorities is mandatory. Anonymity of the subject will be maintained at all times. Sponsor reserves the right to terminate the study for refusal of the Investigator/Institution to supply source documentation of work performed in the study.

13.1 Curriculum Vitae and Other Documentation

All Investigators signing the Protocol and all trial staff should provide a current, signed and dated Curriculum Vitae (CV) to be filed by Sponsor. The CV should include name, title, occupation, education, research experience and present and former positions. A Staff Signature List is required.

14 Investigator Responsibility

Except where the Principal Investigator's signature is specifically required, it is understood that the term 'Investigator' as used in this Protocol and on the CRFs refers to the Principal Investigator or an appropriately qualified member of the staff that the Principal Investigator designates to perform specified duties of the Protocol. The Principal Investigator is ultimately responsible for the conduct of all aspects of the study.
Each Investigator will comply with the local regulations regarding clinical trials and the Investigator responsibilities outlined in the ICH GCP guideline and as per Indian GCP guidelines.

15 Study Report

An outline of the process of preparing, reviewing, audit and approval of the study report should be provided, including the name of the designated contractor if identified / appropriate.

16 Administrative Procedures

16.1 Ethical Considerations

Information on side effects of the test and reference formulations is summarised in the Investigator's Brochure. The monitoring and safety guidelines are outlined in the Monitoring Guidelines for the study. The amount of blood to be sampled in the study is not considered to be excessive in healthy adult subjects. This study will be carried out according to the Declaration of Helsinki, ICMR, GCP, AND the ICH GCP Guidelines.

16.2 Ethical Review Committee :

1. The Protocol will be submitted for approval to IEC, and written approval obtained, before volunteers are recruited and participants are enrolled. The Investigators will receive all the documentation needed for submitting the present Protocol to the IEC. A copy of the respective approval letters will be transmitted to the Study Monitor before starting the study. The composition of the IEC will also be provided to the Study Monitor. If approval is suspended or terminated by the IEC, the Investigator will notify the Study Monitor immediately.

2. It is the responsibility of the Investigator to report study progress to the IEC as required or at intervals not greater than one year.

3. The Principal Investigator, or his/her nominee, will be responsible for reporting any serious adverse events to the IEC as soon as possible, and in accordance with the guidelines of the IEC.

16.3 Regulatory Authorities

- An outline of the process for appropriate regulatory approval should be provided. For example, DCGI approval, CTRI registration.
- Any specific requirements of the regulatory authorities, such as reporting of Serious Adverse Experiences (SAEs) should also be outlined.
- In agreeing to the provisions of the Protocol, these responsibilities are accepted by the Investigator.

16.4 Informed Consent

Before recruitment and enrolment into the study, each prospective candidate will be given a full explanation of the nature and purposes of the study, and a copy of the Subject Information Sheet to review. Once the essential study information has been provided, and the Investigator is assured that each individual volunteer understands the implications of participating in the study, the subjects will be asked to give consent to participate in the study by signing the informed consent form. The consent forms shall be signed and dated by the appropriate parties. The completed consent forms will be retained by the Investigator and a copy of these will be provided by the Investigator to the subject.

16.5 Subject Reimbursement

Each subject will be reimbursed for out of pocket expenses, inconvenience and time involved. Such reimbursement is standard practice in studies. If the study is terminated by Sponsor or the Investigator(s) prior to completion, or a subject withdraws or is withdrawn from the study before completion, a pro-rata payment will be made at the discretion of the Investigator(s).

16.6 Emergency Contact with Investigators

All subjects will be provided with a Subject Emergency Contact Card with contact details of whom to contact in the case of an emergency.

16.7 Notification of Primary Care Physician

With the consent of the volunteer, it is the Investigator's responsibility to notify the primary care physician of the subject's participation in the study, provided that such a physician can be identified for the subject. Documentation of such notification should be maintained by the site for verification by the Study Monitor.

16.8 Investigator Indemnification

Sponsor will reimburse subjects for costs of medical care that occur as a result of complications directly related to participation in this study.

16.9 Financial Aspects

The conduct of the study is subject to a Financial Agreement between Sponsor and the Investigator or Institution.

16.10 : Protocol Amendments

1. Neither the Investigator nor Sponsor will modify the Protocol without first obtaining the concurrence of the other in writing. Protocol modifications that impact on subject safety or the validity of the study will be approved by the IEC.

2. No changes (amendments) to the Protocol may be implemented without prior approval from the Sponsor and the appropriate IEC. If a Protocol amendment requires changes to the Informed Consent Form, the revised Informed Consent Form, prepared by the Investigator, must be approved by the IEC.

3. Once the final Protocol has been issued and signed by the Investigator and the authorised signatories, it shall not be informally altered. .

4. It is the responsibility of the Investigator to submit the amendment to the IEC for their approval; written approval should be obtained and a copy provided to the Sponsor. The Sponsor is responsible for determining whether or not the local regulatory authority must be notified of the Protocol change. Completed and signed Protocol amendments will be circulated to all those who were on the circulation list for the original Protocol.

5. The original signed copy of amendments will be kept in the Study File with the original Protocol. It should be noted that where an amendment to the Protocol substantially alters the study design or the potential risks to the subjects, each subject's consent to continue participation should be obtained.

16.11 Protocol Compliance

1. The instructions and procedures specified in this Protocol require diligent attention to their execution. Should there be questions or consideration of deviation from the Protocol, clarification will be sought from the Study Monitor. Any subject treated in a manner that deviates from the Protocol, or who is admitted into the study but is not qualified according to the Protocol as amended by Sponsor and the Investigator, may be ineligible for analysis and thereby compromise the study.

2. Only when an emergency occurs that requires a departure from the Protocol for an individual will there be such a departure. The nature and reasons for the Protocol violation shall be recorded in the CRF.

3. The Investigator and designees will comply with all applicable state and local laws.

16.12 Archives: Retention of Study Records

All source documents, CRFs and trial documentation will be kept by the Investigator for the appropriate retention period as stipulated by local regulations and ICH-GCP

16.13 Archives: Retention of Other Study Specific Samples

Details should be provided for retention of other study specific samples, such as plasma samples or biopsy samples etc.

17. Reference

18 PROCEDURE of Protocol Writing

18.1 Protocol content and design

Specific content of a protocol will vary depending on whether the subject of investigation is a medicinal product, device or therapeutic intervention. The description below uses the case of a medicinal product, in the case of a device or therapeutic intervention the terms should be adapted appropriately and followed where applicable.

Where the investigator is responsible for the protocol design and /or is the sponsor they must (where applicable) provide the following information in the protocol:

General Information

- Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- Name and address of the sponsor and monitor (if other than the sponsor).
- Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
- Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

Background Information

- Name and description of the investigational product(s).
- A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
- Summary of the known and potential risks and benefits, if any, to human subjects.
- Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- Description of the population to be studied.
- References to literature and data that are relevant to the trial, and that provide background for the trial.

Trial Objectives and Purpose

- A detailed description of the objectives and the purpose of the trial.

Trial Design

- The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

  a. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

  b. A description of the type/design of trial to be conducted (e.g. double-blind, placebo controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

- A description of the measures taken to minimize/avoid bias, including:
  a. Randomization. b. Blinding.

- A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

- Maintenance of trial treatment randomization codes and procedures for breaking codes.

- The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

Selection and Withdrawal of Subjects

- Subject inclusion criteria.

- Subject exclusion criteria.

- Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

  a. When and how to withdraw subjects from the trial/ investigational product treatment.

  b. The type and timing of the data to be collected for withdrawn subjects.

c. Whether and how subjects are to be replaced.

d. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

Treatment of Subjects

- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

- Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

- Procedures for monitoring subject compliance.

Assessment of Efficacy.

- Specification of the efficacy parameters.

- Methods and timing for assessing, recording, and analysing of efficacy parameters.

Assessment of Safety

- Specification of safety parameters.

- The methods and timing for assessing, recording, and analysing safety parameters.

- Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

- The type and duration of the follow-up of subjects after adverse events.

Statistics

- A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

- The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified.

- Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

- The level of significance to be used.
- Criteria for the termination of the trial.
- Procedure for accounting for missing, unused, and spurious data.
- Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
- The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

Direct Access to Source Data/Documents

- The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IEC review, and regulatory inspection(s), providing direct access to source data/documents.

Quality Control and Quality Assurance

Ethics

- Description of ethical considerations relating to the trial.

Data Handling and Record Keeping

Financing and Insurance

- Financing and insurance if not addressed in a separate agreement.

Publication Policy

- Publication policy, if not addressed in a separate agreement.

Supplements

18.2 Amendments to the protocol

The investigator(s) should:
Inform the IEC should seek its approval of amendment to the protocol including amendments that

a. Are proposed or undertaken without prior IEC approval in order to eliminate immediate risks to participants;

b. May increase the risks to participants; or

c. Significantly affect the conduct of the trial.

- inform the IEC as soon as possible of any new safety information from other published or unpublished studies that may have an impact on the continued ethical acceptability of the trial or may indicate the need for amendments to the trial protocol.

18.3 Protocol compliance

The investigator(s) should:

- Conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/ favourable opinion by the IEC.

- Along with the sponsor, sign the protocol, or an alternative contract, to confirm agreement.

- Not implement any deviation from, or changes to the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

- Document and explain any deviation from the approved protocol.

The investigator(s) may:

- Implement a deviation from, or a change to the protocol to eliminate an immediate hazard(s) to trial subjects without prior IEC approval/favourable opinion.

As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

a. To the IEC for review and approval/favourable opinion;

b. To the sponsor for agreement and, if required; and

c. To the regulatory authority(ies).

18.4 Investigational brochure content and design :

Specific content of an Investigational Brochure will vary depending on whether the subject of investigation is a medicinal product, device or therapeutic intervention. The description below uses the case of a medicinal product, in the case of a device or therapeutic intervention the terms should be adapted appropriately and followed where applicable.

The Investigator's Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects.

Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures.

The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial.

The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.

As part of their written application to the IEC provide the IEC with a current copy of the Investigator's Brochure and if updated during the trial, the Investigator/institution should supply a copy to the IEC in accordance with that IEC procedures.

In the case of a marketed product being studied, it may be acceptable to use the Product Information as a substitute for the Investigational Brochure. The ICH guidelines state:

"If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e, a new indication), an IB specific to that new use should be prepared."

18.5 The Investigator Brochure should provide the following information: Title Page

- This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.

Confidentiality Statement :

- The sponsor may wish to include a statement instructing the investigator/ recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IEC.

Contents of the Investigator's Brochure :

- The IB should contain the following sections, each with literature references where appropriate:

Table of Contents

Summary

- A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product or device.

Introduction

- A brief introductory statement should be provided that contains:
- The chemical name (and generic and trade name(s) when approved) of the investigational product(s).
- All active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages).
- The rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s).
- The introductory statement should provide the general approach to be followed in evaluating the investigational product or device.

Physical, Chemical, and Pharmaceutical Properties and Formulation

- A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.
- To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.
- Any structural similarities to other known compounds should be mentioned.

Non-Clinical Studies

Introduction

The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form.

- This summary should address:

a. The methodology used;

b. The results, and a discussion of the relevance of the findings to the investigated therapeutic; and

c. The possible unfavourable and unintended effects in humans.

- The information provided may include the following, as appropriate, if known/available:

a. species tested

b. number and sex of animals in each group

c. unit dose (e.g., milligram/kilogram (mg/kg))

d. dose interval

e. route of administration

f. duration of dosing

g. information on systemic distribution

h. duration of post-exposure follow-up

i. results, including the following aspects:

j. nature and frequency of pharmacological or toxic effects

k. severity or intensity of pharmacological or toxic effects

l. time to onset of effects

m. reversibility of effects

n. duration of effects

o. dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans.

The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

Non-clinical Pharmacology

- A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included.

- Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

Pharmacokinetics and Product Metabolism in Animals

- A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given.

- The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

Toxicology

- A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:
  a. Single dose
  b. Repeated dose
  c. Carcinogenicity
  d. special studies (e.g. irritancy and sensitisation)
  e. Reproductive toxicity
  f. Genotoxicity (mutagenicity)

Effects in Humans

Introduction

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities:

- Where possible, a summary of each completed clinical trial should be provided.

- Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

Pharmacokinetics and Product Metabolism in Humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

  a. Pharmacokinetics (including metabolism, as appropriate, and absorption;)

  b. Plasma protein binding, distribution, and elimination.

  c. Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form;

  d. Population subgroups (e.g., gender, age, and impaired organ function);

  e. Interactions (e.g., product-product interactions and effects of food); and

  f. Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

Safety and Efficacy

- A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients).

- The implications of this information should be discussed.

- In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data.

- Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful.

- Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

- The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

Marketing Experience

- The IB should identify countries where the investigational product has been marketed or approved.

- Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions).

- The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

Summary of Data and Guidance for the Investigator

This section should provide a brief summary of the fundamental requirements or information available for a particular investigational product in order to allow a quick reference for the investigator. Summaries included in this section should not replace the information to be contained in the main body of the document.

Special emphasis should be placed on provision of quick reference safety aspects in order to find information as efficiently as possible.

SOP NO. 12/04 :- Guidelines for investigator initiated research study (IIRS) STUDIES
where only data collection involved and no intervention in patient treatment .

Investigator is the person responsible to the sponsor (if different from himself or herself) and applicable regulatory authorities for the conduct of the research study proposed. (eg. Clinician, Dentist Phd, pharmacist, physiotherapist).

In these cases, the Institutional Ethics Committee (IEC) individually assesses the suitability of the **Investigator's** credentials for the type of study being proposed.

If there is no other organization playing role of Sponsor, Investigator would be considered as sponsor.

Note : All Site SOP's are applicable to IIRS following are specific guidelines. Also note that following guidelines are required for studies that involve studying new drug, device or procedure and all the aspects may not be applicable for observational studies and so Investigators are requested to seek guidance as required for their studies.

Following is sample cover for designing a protocol

CONFIDENTIAL
PROTOCOL TITLE
Protocol No: ----------
Version: ---------Date: ---------

SPONSOR

ADDRESS ----------
Phone: ----------

PRINCIPAL CLINICAL INVESTIGATOR
PRINCIPAL INVESTIGATOR NAME ADDRESS

Phone: ----------

AMENDMENTS:

1.	2.	3.	4.

AUTHORS
NAME
AND ADDRESS OF AUTHOR

STUDY CENTRE
NAME, ADDRESS
AND TELEPHONE NUMBER OF STUDY CENTRE

BIOSTATISTICIAN
NAME AND
ADDRESS OF STATISTICIAN (IF APPLICABLE)

STUDY MONITOR
NAME AND ADDRESS OF STUDY MONITOR

SPONSOR'S MEDICAL REPRESENTATIVE NAME
AND ADDRESS OF
SPONSOR'S MEDICAL EXPERT (if different from investigator)

STUDY ACKNOWLEDGMENT/CONFIDENTIALITY

By signing this Protocol, the Investigator(s) acknowledges and agrees:
The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice[1] (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

Investigator Signatory:

PRINCIPAL INVESTIGATOR – NAME AND TITLE

Signature:

Date

Sponsor Signatory:

SPONSOR SIGNATORY – NAME AND TITLE
Signature: Date

Table of Contents

1 Synopsis

Study Title:

Indication:

No. Subjects:

No. Centres:

Study Duration:

Objectives of the Study:

Study Endpoints: (Primary and Secondary)

Study Design: Eligibility Criteria (Inclusion and Exclusion)

Study Procedures: (Including pharmacokinetic (PK) sampling times)

Safety Parameters/analysis:

Laboratory Parameters/Analysis: Total Blood Volume:

Sample Size Determination: (If applicable)

Statistical Analyses: (Brief Description)

Others :
(As required by the specific study)

2 Introduction

The introduction should outline all the background information and provide a justification for conducting the study in a logical, well ordered fashion.

3 Objectives

A detailed description of the objects of the study should be provided, split in to primary and secondary objectives as appropriate.

4 Study Design

An overview of the study design should be provided. A description of the type/design of the study should be given (i.e. double-blind, placebo-controlled, parallel design, observational e.t.c.), with a description of the population to be studied

5 Study Population

A full description of the study population should be given, including age, sex, condition.

5.1 Number of subjects

The total number of subjects should be provided, along with the number of subjects per specific study cohort if appropriate.

5.2 Inclusion Criteria

All subject inclusion criteria should be listed. Criteria should be specific and unambiguous and outline a population suitable for the phase of the study.

5.3 Exclusion Criteria

All subject exclusion criteria should be listed. Criteria should be specific and unambiguous and should take in to account any cautions and contraindications for the investigational compound(s) and study procedures.

6 Study Assessments and Procedures

All study assessments and procedures should be outlined in a clear, logical and unambiguous fashion. The scientific integrity of the study and the credibility of the data from the trial depend substantially on the study design, and interpretation of the design within the protocol. It is therefore extremely important that the protocol specifically outlines each study procedure in sufficient detail for all procedures to be performed in an identical fashion.

6.1 Screening Evaluation
6.2 Study Procedures
6.3 Efficacy Assessments

All efficacy assessments and procedures should be outlined in detail, or referenced to a separate document or the appendices. Copies of assessment questionnaires should be appended to the protocol.

6.4 Study Restrictions
All study restrictions should be outlined in the section below, together with the duration and period of the study to which the restrictions apply.

6.5 Safety Assessments: (If applicable)
Procedures for all safety assessments should be detailed, or a reference provided for the procedure (e.g. a laboratory handbook etc).

7. Subject Completion and Discontinuation.

7.1 Subject Completion

The definition of a completed subject should be provided.

7.2 Stopping Rules / Discontinuation Criteria

The details and justification of any stopping rules or discontinuation criteria should be provided.

7.3 Subject Withdrawal
Subject withdrawal criteria should be provided, and withdrawal procedures outlined. This should include: When and how to withdraw subjects; the type and timing of data to be collected; whether and how subjects are to be replaced; the follow up process for withdrawn subjects.

7.4 Early Termination of the Study

The study may be terminated prematurely by the principal investigator or his/her designee and criteria should be mentioned for early termination.
.

8. Case Report Form (CRF)

A Case Report Form (CRF) will be completed for each study subject summarising all clinical screening and study data. Subjects will only be referred to in the CRF by their subject number and initials in order to retain subject confidentiality.

9 Data Analysis and Statistical Considerations

9.1Sample Size

The following should be considered and included in this section: Number of subjects planned to be enrolled. In multicentre studies, total no of patients planned and no of patient at KDAH to be specified.

9.2 Statistical Analysis

A description of all statistical methods to be employed, including timing of any planned interim analysis(ses) should be outlined

10 Data Management

An outline of the data management process should be outlined, to include: Where the analysis will take place and how.

11 .1 Ethical Considerations

Protocol should mention This study will be carried out according to the Declaration of Helsinki, ICMR, GCP AND the ICH GCP Guidelines.

11.2 IEC review:

1. The Protocol will be submitted for approval to IEC, and written approval obtained, before volunteers are recruited and participants are enrolled.

11.3 Informed Consent

Before recruitment and enrolment into the study, each prospective candidate will be given a full explanation of the nature and purposes of the study, and a copy of the Subject Information Sheet to review. Once the essential study information has been provided, and the Investigator is assured that each individual volunteer understands the implications of participating in the study, the subjects will be asked to give consent to participate in the study by signing the informed consent form. The consent forms shall be signed and dated by the appropriate parties. The completed consent forms will be retained by the Investigator and a copy of these will be provided by the Investigator to the subject.

11.4 Subject Reimbursement

Each subject will be reimbursed for out of pocket expenses, inconvenience and time involved. (If required, and whenever patient need to come more frequently than routine treatment visits.)

11.5 Financial Aspects

12 . Reference

Acronyms.

ADR – Adverse Drug Reaction
AE – Adverse Event
CDA – Confidentiality Disclosure Agreement
CFR – Code of Federal Regulations (FDA; US)
CIOMS – Council for International Organizations of Medical Sciences
CRA – Clinical Research Associate
CRC – Clinical Research Coordinator
CRF – Case Report Form
CRO – Contract Research Organization
CTA – Clinical Trial Agreement
CV – Curriculum Vitae
DCF – Data Clarification Forms
DCGI - Drug Controller General of India
DSMB – Data Safety Monitoring Board
eCRF – Electronic Case Report Form
EDC – Electronic Data Capture
IEC – Institutional Ethics Committee
FDA – Food and Drug Administration (US)
GCP - Good Clinical Practices
IATA - International Air Transport Association
IB – Investigator Brochure
ICF Informed Consent Form
ICH – International Conference on Harmonization
IB – Investigator's Brochure
ISF – Investigator Study File
IVRS – Interactive Voice Response System
IWRS – Interactive Web-Based Response System
NOC – No Objection certificate
PI – Principal Investigator
QA – Quality Assurance
QC – Quality Control
IU - Investigator Undertaking Form
QOL – Quality of Life
SAE – Serious Adverse Event
SOP – Standard Operating Procedure

Glossary of terms .

Audit: A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, standard operating procedures (SOPs), Good Clinical Practices (GCP) and the applicable regulatory requirement(s)

Audit Report: A written evaluation by the auditor of the results of the audit.

Audit Trail: Documentation that allows reconstruction of the course of events.

Applicable Regulatory Requirement(s): Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Ethics Committee): The documented affirmative decision of the IEC that the trial has been reviewed and may be conducted at the institution sites within the constraints set forth by the IEC, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Adverse Drug Reaction (ADR): In the pre-approval clinical experience with a new investigational product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, eg., the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Biological Product: A product that is derived from living organisms and that is used to prevent, treat or diagnose disease in human beings or animals or for development, experiment or investigation purposes.

Biological Sampling: Collecting, processing and analyzing of biological samples.

Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware, and double blinding usually refers to the participant (s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial participant.

Causality/attribution assessment: Determining whether there is a reasonable possibility that the drug caused or contributed to an adverse event. It includes assessing temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, and the presence (or absence) of a more likely cause.

Central Laboratories: Laboratories used by the sponsor to analyze study specimens in order to ensure validity and consistency in laboratory results.

Clean database (or file): A database from which errors have been eliminated.

Clinical Research Associate (CRA): Person employed by the sponsor, or by a contract research organization (CRO) acting on a sponsor's behalf, who is responsible for determining that a trial is being conducted in accordance with the protocol at the site. A CRA's duties may include, but are not limited to, helping to plan and initiate a trial, assessing the conduct of trials, and assisting in data analysis, interpretation, and extrapolation. CRAs work with the site's clinical research coordinator (CRC) to review all data and documentation pertinent to the trial. Synonyms: monitor, site manager.

Clinical Research Coordinator (CRC): A nurse, health professional or other qualified clinical research team member who handles most of the administrative responsibilities and day-to-day activities of a clinical trial as delegated by the Principal Investigator. The CRC acts as liaison between the investigative site and the sponsor, and ensures review of all data and records before a monitor's visit and performs designated participant assessments. Synonyms: clinical trial coordinator (CTC), study coordinator, research coordinator, clinical coordinator, research nurse, protocol nurse, clinical research associate.

Clinical Research: Any research activities/investigation using human subjects and/or their data. At Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute (KDAH) clinical research studies include, but are not limited to: Regulated Clinical Trials, Quality of Life studies, Qualitative Research, Observational Research,Retrospective Chart Reviews and Database studies involving any patients, healthy normal volunteers, hospital staff and registered students. All clinical research studies must receive IEC approval

Clinical Significance: Change in a participant's clinical condition regarded as important whether or not due to the investigational product. Some statistically significant changes (in blood tests, for example) have no clinical significance. The criterion or criteria for clinical significance should be stated in the protocol.

Clinical Trial: Any investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

Clinical Trial/Study Report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human participants, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

Clinical Trial/Study Materials: Complete set of supplies provided to an investigator by the study sponsor.

Clinical Trial Agreement : A written, signed, and dated agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. At KDAH the CTA are tripartite between the sponsor, KDAH and the PI.

Co-Investigator: A qualified member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions. Synonyms: Sub-investigator.

Comparator (Product): An investigational or marketed product (eg. active control), or placebo, used as a reference in a clinical trial.

Compliance (in relation to trials): Adherence to all the trial-related Good Clinical Practice (GCP) guidelines, and the applicable regulatory requirements.

Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a participant's personal and/or medical information.

Confidentiality Disclosure Agreement: An agreement between the sponsor and the Principal Investigator that prevents the disclosure of proprietary information to anyone other than those directly involved in the clinical trial. Synonym: Confidentiality Agreement.

Contract Research Organization (CRO): An organization (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions. CRO's are independent companies carrying out specialized functions of Pharmaceutical Research and Development such as Phase I, Phase II, Phase III or Phase IV clinical trials.

Clinical trial Registry India (CTRI) : It is set up by the ICMR's national institute of medical Statistics (NIMS) is free and online public record system for registration of clinical trials being conducted in India . DCGI has made has made it mandatory to register trial in CTRI.

Dangerous Goods: A product, substance or organism included by its nature or by the regulations in any of the classes listed within the act:

Drug Controller General of India is responsible for approval of licenses of specified categories of Drugs such as blood and blood products, I. V. Fluids, Vaccine and Sera in India.

Dear Doctor Letter: Notification of a significant safety issues received by the PI. This notification may precede a change in the Investigator Brochure.

Data Clarification Form: A form supplied by the sponsor to make corrections/additions/deletions to previously submitted CRFs and DCFs (synonyms – data queries).

Diagnostic Specimen: Human material, including excreta, secreta, blood and its components, tissue and tissue fluids.

Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, optical, scans, films) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Electronic CRF (eCRF): An electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial participant. Synonyms: Electronic Data Capture

Eligible Patients/Participants: Screened patients/participants who have completed the pre-screening period and have successfully completed all study-specific screening tests and qualify (eg., fulfill the protocol inclusion and exclusion criteria) to be randomized or registered into the study.

Enrolled Patient/Participant: An eligible patient/participant who is randomized or registered into the study.

Enrolment: The process of randomizing or registering an eligible patient/participant into a clinical trial according to the study protocol.

Essential Documents: Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

Exclusion Criteria: A list of criteria, any one of which excludes a potential study participant from involvement in a study. See also inclusion criteria.

Expected Adverse Event: An adverse event that is specified in the investigator's brochure or drug label. Synonym: anticipated adverse event/effect.

Food and Drug Administration (FDA): The United States regulatory authority charged with, among other responsibilities, granting Investigational New Drug (IND) and New Drug Application (NDA) approvals.

Food and Drug Administration (FDA) Regulations: The Title 21, Code of Federal Regulations (21 CFR) represent the USA laws and government agencies regulations for clinical trials. Federal Regulations are the general and permanent rules which are published in the USA Federal Register by the executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas participant to Federal regulation.

Good Clinical Practices (GCP): GCP is an international, ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial participants are protected, consistent with the Declaration of Helsinki, and that the clinical trial data are credible.

Identified Patients/Participants: Patients/participants who have been noted and documented (in compliance with privacy policies) as potentially eligible (eg., satisfy a broad set of eligibility criteria) for a clinical research study(ies); prior to any studyspecific tests or procedures.

Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the ICF and any other written information supplied to the participant. The impartial witness should also sign and date the consent form in addition to the participant or participant's legally accepted representative.

Inclusion Criteria: The criteria that prospective study participants must meet to be eligible for involvement in a study. See also exclusion criteria.

Informed Consent: A process by which a participant voluntarily confirms his or her willingness to enroll in a particular trial, after having been informed of all aspects of the trial that are relevant to their decision to participate. Informed consent is usually documented by means of a written, signed and dated consent form.

Informed Consent Document (ICF): The informed consent form (ICF) is a written form that provides the study participant with information essential to making an informed decision about participating in a clinical trial. The signature of the study participant or the participant's legally authorized representative on the ICF indicates the intent of the participant or the participant's legally authorized representative to give informed consent.

Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Inspector: A designated representative of a regulatory agency who performs the official review of the sponsor or site.

Institutional Ethics Committee (IEC): Committee constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human participants involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants.

International Air Transportation Agency (IATA) - International Air Transport Association. Comprised of member international airlines which establish regulations for uniform safety and interline exchange.

Investigation: Specific response to known or suspected non-compliance. Investigations typically are undertaken when there are reasonable grounds to suspect that noncompliance has occurred and that enforcement measures may be necessary.

Investigational Product: A study drug, biologic, radiopharmaceutical, natural health product, placebo or device being tested or used as a reference in a clinical trial, including a product with marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonyms study drug or study device.

Investigational Product Accountability: The process of being responsible for the investigational product. The PI is responsible for investigational product(s) accountability at the trial site(s).

Investigator-Initiated Trial: A research study that is developed, initiated and conducted by an investigator at a study site. The obligations of the investigator in this case include both those of a sponsor and those of an investigator. Sometimes referred to as local or academic trials. Investigator initiated trials usually start with the development of an investigator initiated research study (IIRS).

Investigator's Brochure (IB): A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human participants.

Investigator Meeting: A meeting organized by the sponsor that brings together all of the Investigators & Study Coordinators conducting the clinical trial and the sponsor representatives such as the Project Manager and Clinical Research Associates assigned to the study. The meeting is held prior to the initiation of the clinical trial. The protocol logistics are discussed and procedures reviewed. Usually an overview of GCP is also provided.

Investigator Study File (ISF): The ISF contains the documents that are usually audited or inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of the data collected. Synonyms: Study File, Regulatory File/Binder, Essential Documents File.

KDAH : Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute is India's newest, most advanced tertiary care facility. As the flagship social initiative of the Reliance Anil Dhirubhai Ambani Group, it is designed to raise India's global standing as a healthcare destination, with emphasis on excellence in clinical services, diagnostic facilities and research activities.

Legally Acceptable Representative: An individual or judical or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's involvement in the clinical trial.

Letter of Indemnification (LOI): An indemnification is a declaration by the Sponsor to legally hold harmless the Institution and PI in the event of legal suit. It can be part of the CTA, or issued as a separate letter. The letter of indemnification must be from the Sponsor.

Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Report: A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

No Objection Certificate (NOC): As part of the KDAH review process, if there have not been any deficiencies identified and the CTA is deemed acceptable, a No Objection Letter (NOC) will be issued by KDAH management clinical services department.

Non-therapeutic Study: A study in which there is no anticipated direct clinical benefit to the participant. (synonym = observational)

Participant: An individual (patient or healthy volunteer) who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.
Synonyms: Study/trial patient, study/trial participant, research participant, subject.

Participant Recruitment: There are numerous strategies that professionals in clinical research can use either broadly or on a study-by-study basis to achieve optimal success in patient/participant recruitment into clinical trials. These strategies relate to the various stages and activities along the recruitment flow chart - from pre-screening to patient/participant enrolment.

Placebo: A pharmaceutical preparation that contains no active agent. In blinded studies, the goal is to make it look, smell and taste just like the active product.

Pre-Screening Period: The portion of the recruitment process prior to the patient/participant signing the consent form.

Product Monograph: A product monograph is a factual, scientific document on a marketed drug product that, devoid of promotional material, describes the properties, claims, indications and conditions of use for the drug, and that contains any other information that may be required for optimal, safe and effective use of the drug.

Project Manager (sponsor*):* The representative of the sponsoring company who has the overall responsibility for the successful planning and execution of a clinical trial.

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP (International Conference on Harmonization). Guideline the term "protocol" refers to protocol and protocol amendments.

Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

Protocol Deviation: An unanticipated or unintentional divergence or departure from the expected conduct of an approved study that is not consistent with the current research protocol, consent document or study addenda.

Protocol Violation: A term broadly used to describe any study event whereby the current IEC approved research protocol was not followed.

Principal Investigator (PI): The person responsible to the sponsor and applicable regulatory authorities for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is a licensed physician .In the case of a clinical trial involving a drug to be use for dental purposes only, the PI may be a physician or dentist. Exception: for an Observational Trial, the PI may be another health care professional (eg. Phd, pharmacist, physiotherapist). In these cases, the IEC individually assesses the suitability of the PI's credentials for the type of study being proposed.

Qualifications: A quality, ability, or accomplishment that makes a person suitable for a particular position or task.

Quality Assurance (QA): All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC): The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomization: The process of assigning trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Recruitment: The processes and activities used to identify patients/participants for clinical trials, from a base population to enrolment into the study.

Recruitment Log: The form/spreadsheet used to record patient/participant activities.

Recruitment Period: Total period of time from initiation of recruitment activities until all participants have been enrolled into a study.

Recruitment Target: Number of patients/participants that must be recruited into a study to meet the requirements of the clinical trial agreement and as submitted to the IEC. In multicenter studies, each investigator has a recruitment target.

Regulatory Authorities: Bodies having the power to regulate. In the ICH GCP guideline, the expression "regulatory authorities" includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities (eg., FDA).

Research: A systematic investigation to establish facts, principles or generalizable knowledge.

Safety Information: Usually in the format of a letter or report from the sponsor or PI indicating that a study participant has experienced an adverse reaction (eg. IND, CIOMS (Council for International Organizations of Medical Sciences) or MedWatch reports)

Screened Patients/Participants: Approached patients/participants who have signed consent form and complete the required study-specific screening tests.

Screening: The study-specific recruitment activities used to determine the final eligibility of a patient/participant for enrolment into a clinical trial, after the informed consent process has been initiated and the patient/participant has signed the informed consent document.

Serious Adverse Event (SAE) : Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. An SAE may include any serious adverse drug reaction.

Shipping Record: A record that relates to study materials being handled, offered for transport or transported and that describes or contains information relating to the goods, and may include electronic records of information.

Site: The location(s) where trial-related activities are actually conducted.
Synonyms: Investigator site

Site Selection Visit: The visit conducted by the sponsor representatives, usually the Project Manager and the Clinical Research Associate (CRA). This visit is conducted before the sponsor selects the site for participation in a clinical trial. Synonyms: Pre- Study Visit.

SOP Author: A member of the clinical research team or SOP committee qualified by experience, skills and training to draft new or revised SOPs.

SOP Authorized Signatory: An approved individual qualified by experience, skills and training to provide final approval of SOPs.

SOP Committee: A group of clinical research personnel representing a broad scope of clinical research areas responsible for the development, revision, review and approval of SOPs.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial. In an investigator initiated research studies (IIRS) the investigator is considered the sponsor.

Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of specific clinical research functions across all KDAH SITES.

Participant Identification Code: A unique identifier assigned to each trial participant to protect the participant's identity and used in lieu of the participant's name when the investigator reports adverse events and/or other trial-related data.

Unblinding: The process whereby the treatment allocation is revealed usually for participant safety or at the study conclusion.

Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg., investigator's brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Unexpected Adverse Event: An adverse event that is not specified in the investigator's brochure or drug label. Synonym: unanticipated adverse event.

Universal Precautions: A set of precautions designed to prevent transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and other blood/ body fluid pathogens when providing first aid, health care or conducting clinical research.

Vulnerable Participants: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable participants include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Waiver: These are single occurrence deviations in inclusion/exclusion criteria. In general they are planned exceptions that should receive sponsor and IEC approval prior to be implemented.