STANDARD OPERATING PROCEDURES FOR CLINICAL TRIALS

❖ Assessing Protocol Feasibility

➢ Purpose

To describe the procedures for assessing the feasibility of conducting a study at Dhiraj Hospital (referred as Site), SVDU in compliance with standard protocol.

Site is committed to maintain the highest scientific, clinical and ethical standards while conducting research at Site. Further, Site is committed to comply with all applicable regulations and guidelines in this regard. In view of the same, before agreeing to participate in a clinical research study, the Principal Investigator (PI) and Institution must agree to the scientific, clinical, and ethical merits of the study; the financial impact to the hospital; compliance with regulations; and the operational feasibility of conducting the study at Site. This standard operating procedure (SOP) describes the steps for assessing the feasibility of conducting a research study at Site.

This standard operating procedure (SOP) describes the steps for fulfilling the regulatory, medical, and ethical requirements for assessing the appropriateness and feasibility of implementing a protocol within the SITE research network.

➢ Scope

This SOP applies to the activities involved in assessing protocol feasibility for all research studies conducted at Site involving human subjects.

➢ Procedure

➢ *Protocol Assessment*

When a Sponsor/CRO contacts the study Site about a potential study, the Principal Investigator (PI) will assess whether or not it would be feasible to conduct the protocol with the existing staff and facilities.

➢ *Clinical/Scientific/Ethical Feasibility*

- Clinical importance to Site patients/subjects.
- Scientific merit.
- Benefits and risks associated with the protocol.
- Consistency with the priorities of the hospital and the clinical department.

➢ *Operational Feasibility*

- Availability of personnel and other resources required to conduct the study.
- Availability of patients meeting the inclusion / exclusion criteria of the study.
- The level of interest expected from the physicians needed to recruit patients into the study.
- The operational complexity of the protocol.
- Whether there are any conflicting studies in progress.

➢ *Regulatory Feasibility*

- The PI reviews the protocol to determine whether there is anything required that may be problematic when submitting the project to the Sumandeep Vidyapeeth Institutional Ethics Committee (referred as SVIEC). As part of the review the Clinical Trial Coordinator (refereed as CTC) can consult with SVIEC representatives.

- The PI must check the following points before submitting the protocol to the SVIEC for approval, as SVIEC determines:
    - Research studies have the resources necessary to protect participants.
    - Adequate time for the researchers to conduct and complete the research.
    - Adequate number of qualified staff
    - Adequate facilities
    - Access to a population that will allow recruitment of the necessary number of participants.
    - Availability of medical or psychosocial resources that participants might need as a consequence of the research.

- ***Financial/ Legal Feasibility***
    - A detailed review of the costs, including staff time needed to complete protocol activities and patient care visits are determined by the PI.
    - The PI and CTC prepare the budget worksheet.
    - The budget worksheet is compared with the sponsor's budget.
    - The PI and CTC will negotiate with the sponsor to establish a feasible budget. Once an agreement is made, the budget will be signed by the PI and sent to the sponsor.
    - If an agreement cannot be reached with the study sponsor to cover all costs of the study, the PI and CTC will work together to determine whether the study will be conducted at SITE.
    - The Legal expert will facilitate legal review of the contract.

➢ Decision

The PI will notify the sponsor (in case of sponsored study) of the Site's decision. In the event that the protocol not meet the above mentioned criteria the convener may, at

his/her discretion, provide rationale for the decision to the PI and PI will inform the same to the sponsor, allowing the Sponsor the opportunity to make changes in the suggested part of the protocol and have it reassessed.

- **Applicable Staff**

This SOP applies to all the personnel's of the clinical research team and the PI and others who may be responsible for making decisions regarding conduct of the research studies at Site.

Communication with Sponsor or Contract Research Organization (CRO):

- **Purpose**

This standard operating procedure (SOP) describes the communication between key research personnel at site and the sponsor/Contract Research Organization (CRO), including telephone and written interactions, during the entire course of a research study conducted at Site and to ensure proper documentation of communications with the Sponsor/CRO concerning study activities.

- **Scope**

This SOP applies to communications between the site and sponsors/CROs involved in the conduct of research study.

These communications serve to protect the safety and well-being of subjects by assuring that studies are conducted compliantly, sponsors/CROs are fully appraised of study site activities, and key research personnel are informed of new information about the study provided by the sponsor/CRO.

Any new study which initiated during active period of the SOP will be covered under the SOPs, unless otherwise indicated. If necessary a study specific SOP may be prepared.

➢ Procedure

General communications

- Provide the sponsor/CRO a contact list of site personnel involved in study start up, along with each individual's role and responsibilities.
- Communicate regularly, courteously and in accordance with Site standards, with the sponsor/CRO about all study related issues.
- Be familiar with the sponsor's SOPs pertaining to communications, including reporting timelines and preferred communication mode.
- Keep originals or photocopies of all study-related communications, including faxes with corresponding confirmations, e-mails, and written summaries of phone conversations.
- File all communication documents in the appropriate section of the Site Master File.
- Retain all sponsor-generated communications regarding conduct of the study (e.g., teleconference announcement) in the correspondence section of the Site Master File. Budget, payment and other contractual or financial communications should be filed separately from the regulatory binder. Ensure information is communicated to the Principal Investigator (PI) and other key research personnel as applicable.

Pre-Study communication

- The Clinical Trial Coordinator is responsible for sending the Confidentiality Agreement to the sponsor/CRO once reviewed and signed by PI.
- Notify the sponsor/CRO of the PI's decision to conduct the research study at Site.
- Review the protocol and submit if any questions concerning interpretation of the protocol or conduct of the study to the sponsor/CRO in writing and file the copy in the Site Master File.

- Fill the questionnaires provided by the sponsor/CRO regarding the study related requirements.
- Prepare questions to clarify protocol procedures, subject eligibility criteria, and other study-related issues in writing and file the reply in the Site Master File.
- The PI/Co I will discuss how the site is equipped to perform the study. This discussion will include a description of the potential subjects available for the study and methods being considered for recruitment.

Communications while the study is ongoing

- Investigator/Clinical Trial Coordinator will submit the updated screening and/or enrolment logs to the sponsor/CRO by the preferred mode of communication.
- Notify Sponsor/CRO about unanticipated issues, including adverse events (AEs) and Serious Adverse Events (SAEs), per the sponsor's definitions and timelines, as defined in the protocol or SOP.
- Communicate protocol deviations, as they occur, according to the sponsor requirements.
- Submit completed CRFs (paper-based or e-CRF) to the sponsor/CRO in accordance with the Clinical Trial Agreement (CTA).
- Respond promptly to data queries as requested via fax, e-mail, and/or direct electronic data capture resolution, per the sponsor's requirements and document the same in the specified Site Master File.
- Communicate significant regulatory changes as per the sponsor's requirements (e.g., SEC acknowledgement of an unanticipated issues or protocol deviation, SVIEC approval of a revised consent document, etc.). Typically these documents are reviewed during interim monitoring visits; however specific sponsors/CROs may require prompt notification in specific circumstances.

- Submit sponsor-generated protocol amendments to the SVIEC. Once approval is obtained, PI will train the study team regarding the changes prior to implementation and same will be documented and informed to Sponsor/CRO
- Forward safety reports received from the sponsor (e.g., off-site SAE/SUSAR) to the PI who will review the event and report to the SVIEC as per SVIEC SOP. Notification of other key research personnel and/or enrolled subjects may be necessary (e.g., new risk identified related to investigational treatment).

Communication after study is completed

- Inform SVIEC regarding scheduled site close out visit.
- Communicate with sponsor and confirm the close out date.
- Provide the sponsor/CRO with any SVIEC required correspondence (e.g. information requires in the SVIEC study closure letter) related to the study close out.
- Ensure that all close out activities are performed and all sponsors requirements are met.
- After receiving the final close out letter and study result from the sponsor, submit the same to the SVIEC in the required SVIEC format.
- File all the communication in the appropriate section of the site master file.

➢ Sponsor Contact

1. Telephone Contacts – All study personnel will document critical conversations with the Sponsor/CRO in the source notes, especially those pertaining to eligibility criteria, protocol deviations, and serious adverse experiences. If requires the Clinical Trial Coordinator or delegate will file the Telephone Contact copy in the Site Master File.

2. Letters and Faxes – All study personnel will make copies of all correspondence written to the Sponsor/CRO. The Clinical Trial Coordinator or delegate will file this correspondence in the Site Master File.
3. e-mails – All study personnel will print out copies of critical e-mails with the Sponsor/CRO. The Clinical Trial coordinator or delegate will file this correspondence in the Site Master File and if required in the source notes.

At a minimum, the Sponsor/CRO should be notified:

- When the first subject is enrolled in the study.
- When there is a question concerning a potential subject's eligibility.
- When recruitment issues occur.
- When a protocol violation occurs.
- When an SAE occurs.

➢ Applicable Staff

This SOP applies to all the personals of the clinical research team involved in communication with the Sponsor/CRO and responsible for the management of the data.

These include the following:

- Principal Investigator
- Sub Investigator
- Clinical trial coordinator
- Pharmacist
- Support Staff

Interaction with Institutional Ethics Committee:

➢ Purpose

To describe the procedures related to communication with the Sumandeep Vidyapeeth Institutional Ethics Committee (SVIEC) during the entire study duration right from study initiation to completion, and to describe what documents should be retained to reflect interaction with the SVIEC.

➢ Scope

This SOP will apply to all studies being conducted at Site.

➢ Procedure

Interactions with the Sumandeep Vidyapeeth Institutional Ethics Committee (SVIEC) continue throughout the duration of a research study. Establishing effective ongoing SVIEC communication and reporting procedures are essential to the successful management of research studies. An effective working relationship with the SVIEC strengthens the team approach to the protection of participant safety in addition to enhancing compliance with applicable SOPs, guidelines and regulations governing research studies.

Interaction with SVIEC required during the entire course of the research study, the phases could be:

➢ **Initial Submission of project to SVIEC**

i. **Detailed description of project submission**

- The PI/ Co-I/CTC should submit all study related documents to the SVIEC, no fewer than fourteen (14) days before the scheduled meeting.
- The PI/Co-I/CTC should complete the SVIEC submission form (Refer SVIEC SOP) and PI must sign and date in the form wherever required.

- PI/Co-I/CTC must check the submissions as per the SVIEC checklist (Refer SVIEC SOP) to ensure that all mandatory forms and documents are enclosed.
- The CTC will submit the signed forms and documents to the SVIEC. These include, but are not limited to:
    - Covering letter with brief description regarding the list of documents enclosed for SVIEC approval, including the no. of copies submitted, document enclosed relevant version number and date of all the documents.
    - Project submission Form as mentioned above
    - Study protocol
    - Other related documents necessary for initial review as mentioned in the SVIEC
    - Curriculum Vitae and updated GCP certificate of the investigator and study team.
    - SVIEC fees cheque in the favour of "SoniyaKhanna", in case of sponsored studies.
    - Number of copies required for SVIEC submission will be as per SVIEC SOP.

Note: One additional copy for PI Acknowledgement.

The PI/CTC should keep a copy of the acknowledged (SVIEC stamp with sign and date) submission letter of the above mentioned documents in the Site Master File (SMF) and send scan or copy to the sponsor (via mail or courier as required by the sponsor).

PI/CTC must document the unique "Project no." given by the SVIEC after project submission for future communication and collect updated SVIEC membership roster and SVIEC registration number and should place in the Site Master File (SMF).

ii. EC Response

The PI and CTC should ensure that the letter of response from the SVIEC includes the following information:

- Clinical study identification, protocol number and title;
- Name and version date of all documents reviewed by the SVIEC.
- Date of review by the SVIEC
- Approval for the number of participants to be recruited in the study.
- Decision/opinion/approval of the clinical study, including required modifications, ifany; (Note: Reply to the SVIEC in case of any suggested modifications)
- If conditional approval given, it is not valid for more than 6 months (Refer SVIEC SOP)
- Procedures for appealing the decision/opinion of the committee;
- Any other information, if applicable, as described in the SVIEC SOP
- Date of renewal of approval;
- Signature of the SVIEC member secretary and date of the response.
- Following Schedule Y and GCP (ICH 3.2.1 & 3.2.2) a list of the members of the Ethics Committee and their qualifications, as well as the procedures of the said committee should be available.
- The PI/CTC should keep an original copy of the SECs approval letter in the SMF and provide one copy to the sponsor/CRO (via email/fax).
- Immediately after receiving SVIEC approval, register the study on CTRI and if applicable on ClinicalTrials.gov
- Notify SVIEC after receiving registration number.

➢ Study Progress

PI can start project at site after receiving approval letter from SVIEC and as study progress at site PI must communicate with SVIEC for all required notification and reporting such as:

➢ Protocol Amendments

a. *Major Amendments*

- Notify the SVIEC of any changes to the protocol and/or informed consent and/or of new information on the investigational product no fewer than fourteen (14) days before the next scheduled meeting.
- All amendments should bear amendment number and version number with date(s).
- CTC must make sure that all changes or modifications in the amended version are underlined or highlighted along with detailed summary of changes.
- The amendment /documents along with the covering letter should be accompanied by Amendment Reporting Form (Refer SVIEC SOP)
- Number of copies required for SVIEC submission will be as per SVIEC SOP
- Note: One additional copy for PI Acknowledgement
- The PI/CO-I/CTC should obtain a copy of the acknowledged (SVIEC stamp with sign and date) amendment submission letter of the above mentioned documents, and file the same in relevant section of SMF and send Scan or a copy to sponsor/ CRO(via email/fax).
- The amendments in the protocol and/or informed consent and of new information on the IP will be valid only after SVIEC approval, and should immediately implement the documents at the site after approval.
- Document the approval letter in the relevant section of the SMF and send a copy to sponsor/CRO(via email/fax)

b. Minor amendments and notifications

Minor amendments are those that do not increase the risk or decrease the potential benefit to subjects and may be approved by the SVIEC (Refer SVIEC SOP).

This may include but may not restrict to:

- Renewed insurance policy
- DCGI and DGFT approvals
- Administrative notes
- Documents of administrative nature

➢ **Deviations/Violation and Waivers**

- Submit protocol deviations/violations and waivers to the SVIEC for review and approval according to SVIEC and regulatory requirements
- Deviation/ non-compliance/ violation/waiver happens at site, when investigators/trial sites, fail to follow the procedures written in the approved protocol
- comply with national / international guidelines for the conduct of human research
- fail to respond to the SVIEC requests
- PI/CO-I//CTC must submit the deviations /violations/waiver reports as per the SECSOP.
- Protocol deviation/ non-compliance/ violation/waiver can be detected during monitoring visit for the investigator initiated study by SVIEC and for sponsored studies by the monitor/ CRA also. Sometimes it can be detected by PI /study team member.
- The SVIEC members and/or monitor/ CRA performing monitoring of the project a tstudy site can detect protocol deviation/non-compliance / violation, if the project is –

- not conducted as per protocol / national / international regulations
- when scrutinizing annual / periodic reports / SAE reports
- fail to respond to requests from SVIEC within reasonable time limit
- fail to adhere to protocol required procedures

- Protocol Waiver is analogous to a Protocol Deviation, except that prior SVIEC approval must be obtained before implementing the necessary departures from the protocol. Therefore, Protocol Waivers are anticipatory, while Protocol Deviations are not. E.g. Protocol Waiver means a prospective decision by a sponsor or investigator to permit accrual of a subject who does not satisfy the approved inclusion /exclusion criteria for enrolment.
- SVIEC action could include one or more of the following:
  - SVIEC will inform the PI that SVIEC has noted the violation / noncompliance /deviation and inform the PI to ensure that deviations / noncompliance / violations do not occur in future and follow SVIEC recommendations.
  - SVIEC will enlist measures that the PI would undertake to ensure that deviations /noncompliance /violations do not occur in future.
  - call for additional information
  - Suspend the study till additional information is made available and is scrutinized
  - Suspend the study till recommendations made by the SVIEC are implemented bythe PI and found to be satisfactory by the SVIEC
  - Suspend the study for a fixed duration of time
  - Inform the Director, SITE
  - Revoke approval of the current study
  - Inform DCGI / Other relevant regulatory authorities
  - Keep other research proposals from the PI/ Co-PI under abeyance

- Review and / or inspect other studies undertaken by PI/Co-PI

- File the SVIEC acknowledged deviations/violations and waivers forms submitted in relevant file and send one copy to the sponsor/CRO.

➢ Safety Information

- Safety information can be any information recently reported or obtained from sponsor/CRO particularly regarding risks associated with the research.
- Safety information is categorized as Serious Adverse event (SAEs) and unexpected event reports of both onsite and offsite.
- The Principal Investigator must review safety information received from the sponsor.
- It is recommended that the PI review of safety information must be documented.
- The Investigator must submit Serious Adverse Events (SAEs) and unexpected events reports, both onsite and offsite, including follow up reports for active study participants.
- Report all safety information to the SVIEC according to the SVIEC and regulatory requirements (eg. Investigational New Drug [IND] submissions, Council for International Organizations of Medical Sciences [CIOMS] reports, Suspected Unexpected Serious Adverse Reaction (SUSAR), Periodic Safety Update Report(PSUR), Data Safety Monitoring Board [DSMB] reports).
- File the safety reports and any associated SVIEC correspondence, if any, in the SMF.
- Copies of the associated SVIEC correspondence should be provided to the sponsor according to sponsor requirements.
- Report any other information to the SVIEC that may adversely affect the safety of the participants or the conduct of the research study.

a. Off Site Safety Reports

- Off Site SAEs are adverse event reports that are serious, expected, unexpected related and unrelated (definitely, probably and possibly) to the drug and need prompt reporting to the SVIEC/DSMSC/Sponsor.
- The SAEs that are expected (if listed in the informed consent and IB) or unexpected but unrelated to the drug (classified as per the Offsite SAE Classification form – asper SVIEC SOP) have to be logged by the PI and to be submitted timely. The following log will be maintained continuously until the end of the study.
- SVIEC/DSMSC will accept the log of the SAEs every 3 months and/or at the time of continuing review/ annual status report.
- Those off site SAEs which qualify for prompt reporting, (classified as per the Offsite SAE Classification form – as per SVIEC SOP) will be reported to SVIEC /DSMSC
- Sponsor/CRO will send two sets of the offsite SAE, CTC will submit one to the SEC/DSMSC (as per the SVIEC SOP) and file acknowledged (Stamped, signed and dated by the SVIEC /DSMSC) copy in the SMF and send a copy to the sponsor/CRO.
- PI's must review the SAE listings in detail and report if a trend is observed and communicate the same to SVIEC/DSMSC.
- PI/Co I may receive email or letter as applicable, if any queries are raised by the SEC/DSMSC Secretary. PI/Co I must reply to the query immediately.

b. Onsite SAE reporting:

Kindly Refer SOP for Safety Reporting

➢ Annual Report/ Continuing Review report

- The purpose of Annual report/ continuing review report is to monitor the progress of the study which was previously approved; not only for the changes but to ensure continued protection of the rights and welfare of research subjects.
- PI/Co I/CTC must submit continuing review report/annual report to the SVIEC annually, subsequent to the date of SVIEC approval to renew approval before two months of expiry.
- All information must be provided to SVIEC/DSMSC, as requested in the continuing review application form (Refer SVIEC SOP)
- The Investigator/CTC should submit the continuing review application well in advance i.e. 12 months after SVIEC final approval.
- CTC should submit three hard copies of the report (1+2) and a soft copy.
- CTC should obtain a copy of the annual/continuing review report acknowledged by SVIEC, and file the same in SMF and send a copy to sponsor (via email/fax).
- The SVIEC Secretary will notify Principal Investigator in case committee recommended modifications, and PI will be requested to resubmit the relevant documents within 1 month for the approval till then the project is suspended.
- Principal Investigator will be communicated about the decision within 14 working days after the minutes are finalized.
- The PI will receive a letter from SVIEC/DSMSC, if the continuing review report/annual report is approved / accepted.
- The letter should be file in the SMF and a copy should be provided to the sponsor.

Note: If there is delay in approval of the continuing review report subsequently from the date of SVIEC approval, the PI cannot recruit any patient during that phase, till SVIEC/DSMSC, approve the continuing review report.

➢ Study Termination

a. Premature Termination / Suspension /Discontinuation of the study

- Research studies are usually terminated as per the recommendation of the SVIEC,PI, Sponsor or other authorized bodies wherein subject enrolment and subject follow-up are discontinued before the scheduled completion of the study.
- The SVIEC/Sponsor/PI/ other authorized bodies can prematurely terminate the study for the following reason but not limited to:
    - Protocol non-compliance/violation due to any reason.
    - Slow recruitment
    - Frequency of SAEs occurring at trial site may require the study to be prematurely terminated for the safety of the patients.
    - Sponsor find treatment not effective
    - Lack of funds, lack of adequate market potential, competing drugs have received marketing approval ahead of the test compound, etc.
    - Overall trial enrolment was met, so all sites are being closed, even if some sites have not completed their enrolments.
- Based on the above mentioned reasons SVIEC secretary can send a notification letter for termination/suspension/discontinuation or query letter to request additional information to the PI.
- In case Sponsor is terminating the study, PI will receive a letter from Sponsor/CRO for the termination/suspension/discontinuation with the explanation for the same.

- PI and CTC will prepare the protocol termination package along with covering letter, Premature Termination Report (Refer SVIEC SOP) signed and dated by PI and another material (e.g. letter received from the Sponsor/PI/SVIEC)
- CTC must obtain acknowledgment of the SVIEC member secretary on the covering letter and file it in the SMF.
- PI/CTC must reply immediately in case of any query generated or any further information requested from the SVIEC.
- PI will receive acceptance letter from the SVIEC, CTC will keep the original letter of the Premature Termination/suspension/discontinuation report in the study file and send the file to archive (Refer SOP; Archival of Essential Documents). Inform the same to Sponsor/CRO.

➢ Study completion

- On the Study completion the PI/ CTC will notify the SVIEC of the study completion using study completion form (Refer SVIEC SOP)
- Additionally PI and CTC must submit letter provided by the sponsor/CRO to give adequate and sufficient information.
- CTC must submit one hard copy + soft copy of Study Completion Reports

➢ Applicable Staff

This SOP applies to all the personals of the clinical research

These include the following:

- Investigator
- Research Team (listed in the delegation log)
- CTC
- SVIEC staff/member

➢ Managing Biological Samples:

➢ Purpose

This SOP describes the procedures for collection, preparation, storage and shipment of biological sample

➢ Scope

This SOP will apply to all biological samples collected, processed, stored and shipped by SITE, unless alternate directions are provided by the sponsor or Contract Research Organization (CRO).

➢ Procedure

- **Collection of Samples**

  Study Nurse or the person delegated in the duty delegation log will collect the biological samples on scheduled visit as described in the protocol.

  After collecting the sample, the study nurse or delegated person will record the details in the biological sample collection form

- **Preparation of Samples**

  - The sample either is stored as collected and/or processed as mentioned in the protocol or laboratory manual provided by the sponsor/CRO.
  - Using a permanent marker, study nurse or CTC will record the patient initials, patient ID and the date and time when the sample was obtained on each sample labels.
  - In case of any damage to sample or if samples is unusable immediately inform to Sponsor/ CRO (in case of sponsored study) and report deviation to SVIEC and document the same in the source note, if required.

- **Storage of Samples**
  - Before shipments, site personnel will store both urine and plasma samples at a temperature of at least - 20ºC – or at a temperature mentioned in the protocol
  - Other biological samples should be stored as mentioned in the protocol.

- **Shipment of Samples**

  Site personnel will

  - Call the courier person as agreed by the sponsor/as mentioned in the protocol and schedule the date and time for shipping the sample.
  - Inform the courier person to bring the required materials for shipment as mentioned in the protocol.
  - Complete all the biological sample inventory form available in the collection kit listing all the samples in the shipment.
  - Keep a photocopy of the Biological Sample Inventory page in the TMF.

Applicable Staff

This SOP applies to all the existing personals of the clinical research team and any new member appointed who may be responsible for study related activities as mentioned in this SOP(per the delegation log). These include following

- Investigator
- Research Team (listed in the delegation log)
- Study Nurse

Managing Investigational Products (IPs):

Purpose

To describe the process and requirements for the receipt, storage, dispensing, and return or destruction of Investigational Product (IP) at site.

➢ Scope

This Standard Operating Procedure (SOP) will apply to all studies being conducted at SITE. Any new trial which is initiated during active period of the SOP will be covered under the SOPs, unless otherwise indicated. If necessary a study specific SOP may be prepared.

➢ Procedure

Prior to receipt of Investigational Product (IP)/ Study Drug

- PI must identify an area with restricted access and appropriate temperature control for IP storage. This is area will be known as 'IP Storage Room'.
- Assign team members who would be responsible for IP receipt, storage, dispensing, accountability and recording the temperature for the storage area and returning or destruction of the IP/ study drug.
- The person must be identified on the study delegation log.

➢ Receipt of Investigational Product (IP)/ Study Drug

- Upon receipt of the IP shipment at the site, the CTC/delegated member will unpack the IP box and check the IP inventory against the shipping form.
- Checking the inventory will include the following:
    - Checking the packaging numbers
    - Unique Kit numbers/IP number
    - Lot/batch numbers
    - Number of IPs in the container (s)
    - IP expiry date
- Any discrepancies (e.g. tampering/ breakage of the IP kit, mismatch in the number of kits, temperature excursions etc.) identified must be documented and informed

to the sponsor/CRO point of contact immediately and seek advice for the next steps.

- Such IP must be stored separately and must be dispensed only after confirmation from the sponsor/CRO/designee. This must be done by the person designated for IP accountability.
- If the inventory matches the drug received, the pharmacist/delegated person will sign and date (note: mention logger temperature present in the IP container on the receipt form) on the shipping receipt or Investigational Product Receipt Form, return a copy to the sponsor, and file the original in the Trial Master File (SMF).
- Shipment inventory must be done as per the study specific procedure (e.g. IVRS or IWRS, accountability log etc.)
- The IP must be immediately transferred to the designated storage area at conditions as mentioned in the protocol.
- The temperature of the storage area must be recorded with a calibrated thermometer for the temperature range once daily or as mentioned in the protocol. It is strongly recommended that accurate temperature must be recorded.
- If available maintain the hard copy of auto generated temperature logger.

➢ IP / Study Drug Storage

- Temperature of the IP storage area must be maintained on a 24-hour basis for recording temperature. The temperature will be recorded once daily or as mentioned in the protocol, except on holidays and Sundays. The capture of minimum and maximum values of temperature will be recorded if only specified by the sponsor/CRO.

- In case a temperature excursion is noted, the CTC/designated study team member must inform Investigator and the following telephonically followed by email at the earliest:
    - Inform the sponsor / CRO and document the same
    - Try to identify the cause of temperature excursion
- Take remedial actions in consultation with sponsor/CRO
- IP that has undergone a temperature excursion must be kept separately and must not be dispensed till a confirmation from sponsor/CRO is obtained i.e. the IP is "fit for use".

➢ IP / Study Drug Dispensing

- IP must be dispensed by the CTC/delegated member to subjects randomized on the study after fulfilling the eligibility criteria in accordance with the protocol.
- Upon dispensing the IP the CTC/delegated member must note following in the source note and IP package:
    - Trial/Study ID number (both source notes and IP package)
    - Initial of the subject (both source notes and IP package)
    - Date of IP dispensing (both source notes and IP package)
    - Batch number and quantity of IP dispensed (in the source note)
    - Expiry date (in the source note)
    - This information must be captured in Real time basis on the IP stickers available on IP containers, in the subject source notes as well as in the Drug Accountability Logs.
- The CTC/delegated member will maintain a record of drug dispensed to and retrieved from each subject. To accomplish this, the CTC/delegated member will use the CRF, if any and only if provided by the sponsor/CRO.

- The CTC/delegated member will explain to each subject the drug accountability needs for
- The study (e.g., the need for the subject to return unused, partially used, and empty packages).
- Requests for IP resupply must be done as per the study specific procedures.

➢ IP/ Study Drug Return

- The study subject will return all drug and study-related supplies to CTC/delegated member on the specified visit mentioned in the protocol.
- The CTC/delegated member will count the returned drug and compare this with the amount of drug expected to have been used since the previous study visit.
- CTC/delegated member must document IP returned by the subject in the subject's source file as well as in the drug accountability logs as per the study requirement.
- In case of missing IP or extra IP, the CTC/delegated member must obtain the information from the Subject and document the clarification provided in the source notes, drug dispensing log and CRF. This documentation should be done in real time basis
- The CTC/delegated member will keep the Drug Dispensing Log and the drug accountability CRF pages updated, regardless of when the monitor will perform final accountability.
- The CTC/delegated member will store the returned drug separately in a secure area until it is verified by the CRA/Monitor.
- Whether the drug is to be returned to the sponsor or destroyed on-site will be determined by the instructions in the protocol.
- The documentation of the destruction/ return must be maintained in the SMF.

➢ Return of IP to Sponsor

- As specified in the protocol, the IP will be returned to the sponsor at intervals or at the end of the study. The CTC/delegated member will follow the protocol or other instructions from the Sponsor or CRO to decide whether empty containers must be returned.
- The CRA/Monitor will perform the independent drug accountability review and will seal the drug that need to be shipped back to the Sponsor/CRO.
- The CRA/Monitor will arrange the preferred courier for the shipment of used and/or unused IP back to the sponsor/CRO.
- The CTC will arrange for a gate pass for the shipment that needs to send back to sponsor/CRO.
- Unless instructed otherwise by the CRA/Monitor, the CTC/delegated member will:
- Perform an inventory of the drug supplies.
- Compare inventory with the study medication records.
- Document discrepancies in the CRF or in a memo to file.
- Complete the Drug Return/Destruction Form (in presence of monitor) or similar form provided by the sponsor or CRO.
- Include a copy of the signed and completed Drug Return Form with the drug shipment and place the original in the study file.

➢ IP Record Retention

At study completion, the CTC will file all drug records with other regulatory documents in accordance with the record retention policy mentioned in the protocol.

➢ Applicable staff

This SOP applies to those members of the study team involved in the process receipt, storage, dispensing, and return or destruction of Investigational Product (IP).These include the following:

- Principal Investigator (PI)
- Clinical Trial Coordinator (CTC)
- Pharmacist
- Research Nurse
- Support Staff

➢ Travelling Reimbursement to Study participants:

➢ Purpose:

This SOP describes the procedures involved in reimbursement to the study subject for their involvement in the research and research related activities as agreed in CTA and mentioned in ICF.

➢ Scope

This SOP applies to all study team member who are engaged in study related activities and delegated in the delegation log for research related reimbursement (if applicable) to all subject participated in the studies being conducted in Site.

➢ Procedure

Information regarding reimbursement

Subjects may be paid for the inconvenience and time present, and should be reimbursed for expenses incurred, in connection with their participation in research. They may also receive free medical services. However, payments should not be so large or the medical

services so extensive as to induce prospective subjects to consent to participate in research against their better judgment (inducement). All payments, reimbursement and medical services to be provided to research subjects should be approved by the SVIEC. Care should be taken:

- When a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses;
- When a subject is withdrawn from research for medical reasons related to the study the subject should get the benefit for full participation;
- When a subject withdraws for any other reasons he/she should be paid in proportion to the amount of participation.
- Reimbursement must be done as agreed by the investigator and sponsor/CRO in the Clinical Trial Agreement (CTA) and as defined in the Informed consent document.

Procedure for reimbursement

CTC as designated will reimburse the amount to the patient as mentioned below:

- Should open a particular study account in the SITE accounts department and maintain the account number. Always deposit the cheque in the same account received by the sponsor/CRO.
- Keep a track of patient's visits as mentioned in the protocol, travel, concomitant medication prescribed for adverse event (if any), and if any unscheduled visit scheduled during the study period for reimbursement.
- Must reimburse travel cost, upon presentation of receipt of a valid ticket (if available or as agreed in the CTA) or bills of the protocol specified visits or unscheduled visits if any.

- Must collect the original bills from the patient for above listed things for reimbursement
- Payment voucher must be prepared for the same; it will include patient hospital case number, name, amount to be paid, study account number and reason for reimbursement.
- Investigator or designee will approve and sign the voucher. Patient will sign or put his/her thumb impression in case patient is illiterate on the copy of the voucher (patient will sign/thumb while submitting the voucher to the accounts department).
- Copy of signed voucher (by investigator/designee and subject) and bills should be filed in a separate file.
- Original voucher and bills will be forwarded to the concerned authority as per the hospital policy for approval.
- The voucher and bills will be forwarded to the accounts department of the SITE.

The competent authority from accounts department will sanction and release the amount.

In case of Serious Adverse Event (SAE) which found to be related to the IP, PI/ Co I will make sure that subject should get reimbursed for every expense occurred during the management of the adverse event.

CTC will always keep a copy of the updated account statement to make sure the account has sufficient balance for reimbursement.

CTC should send the expense invoices to sponsor on regular intervals, to receive the amount on time.

➢ Applicable Staff

This SOP applies to all the existing personals of the clinical research team and any new member appointed who may be responsible reimbursing the study subject as mentioned in this SOP (as per the delegation log).

These include the following:

- Investigator
- CTC
- Research Team (listed in the delegation log)

➢ Site Initiation, Activation, Conduct and Closeout

❖ Purpose

To describe the process, that ensures that the site is organized and prepared for the proper conduct of the research study at SITE. This standard operating procedure (SOP) also describes the processes to be followed at site initiation, activation, conduct and closeout of research study at Site.

❖ Scope

This SOP will apply to all Pharma sponsored research study initiation, activation, conduct and close-out at Site.

❖ Procedure

A research study should be initiated at a site only after investigator and Sponsor/CRO involved in the study is satisfied that essential documents, agreements and approvals are all in place. The site initiation process is designed to ensure that;

- Site has all essential documents in place for the site to conduct the study in compliance with the approved protocol and applicable regulatory guidelines.
- Site is aware of all the sponsor's procedures and SOPs for study conduct (such as

safety recording and reporting, amendments, notification of any urgent safety measures/ violations or serious breaches) and has read and understood each.

- Site is met with all the required regulatory and sponsor requirements.

➢ Preparing site for Site Initiation Visit

For preparing the site for initiation the investigator(s) or Clinical Trial Coordinator (CTC) should:

- Confirm the available date and time with the clinical research team that must attend the meeting and arrange the most suitable meeting date, time and place.
- Request an agenda for the visit from the sponsor; circulate the same to each team member.
- Confirm that investigator and team has reviewed the Protocol and Investigator's Brochure (IB) and any up-to-date information on investigational product (IP). The Investigator(s) must prepare a list of questions if any to be asked in the SIV.
- Ensure that the procedures stated in the study protocol are applicable at the site and fully understood.
- Confirm that all documents required by Institutional Ethics Committee (SVIEC) are available.
- Confirm that the clinical trial agreement (CTA), indemnification letter and budget are finalized and signed.
- Notify appropriate departments regarding the sponsor/CRO visit (e.g., Laboratories, pharmacy, CT scan, bone scan and x-ray, etc).
- File all essential documents in TMF (or sponsor-supplied Investigator Study File), and compile any outstanding documents to provide to the Clinical Research Associate (CRA) at the initiation meeting.

➢ During the Site Initiation Visit

a. During the initiation visit the investigator(s) or Clinical Trial Coordinator (CTC) *should ensure that -*

- The Investigator's Trial Master File (TMF) contains the following mentioned applicable items and all the required regulatory documents:
    - Signed protocol and Investigator Statement
    - Signed and executed Investigator contract
    - CVs and licenses of key site study staff
    - Financial Disclosure forms
    - Investigator Undertaking (IU)
    - SVIEC approval letter for the protocol
    - SVIEC membership roster (updated)
    - SVIEC approved informed consent form
    - Institutional and/or other regulatory authority approvals
    - Valid clinical/other laboratory licensure
    - Laboratory normal value ranges
    - Notice that indicates the study has been submitted to the regulatory authorities (if applicable).
    - Investigator Brochure, if applicable.
    - Case Report Forms (CRF)
    - Investigational product inventory management forms
    - Any other essential documents.
- Provide the study members name involved in the study and their responsibilities in the duty delegation to the monitor/CRA.

- Provide original and updated curriculum vitae of all study personnel / Investigators involved, as per sponsor requirements (if not provided earlier).
- Ensure that the names and contact numbers of the relevant medical and study personnel of the sponsor are available and documented clearly.
- Ensure that all relevant study site personnel fill out the Site Personnel/Signature Log and Training Log.
- Check that the procedures and plans for storage, dispensing and return of IP have been agreed and finalized with the Sponsor and Pharmacist (if applicable).
- In case of paper CRF's: Check that the quantity of CRFs that have been requested or shipped to the study site are sufficient for the number of Participants/patients that are likely to be recruited into the study also allowing for the archiving of one set of intact, unused CRFs
- Check that other related supplies are available or are to be shipped to the study site at a later date, and that they are available in sufficient quantities.
- Check that laboratory facilities and arrangements for the dispatch of samples to the central laboratory are organized and that any specialized equipment that may be required will be available throughout the period of the trial, e.g. collection kits, centrifuge machine, freezer, etc.
- Ensure that monitor/CRA gives sufficient time to CTC for CRF completion training.
- Ensure and understand the requirements of the sponsors/CRO regarding source documents and raw data, which will be required during monitoring visits to enable the monitor/CRA to perform source data verification at each monitoring visit.
- Ensure that the procedures relating to the archiving of study records at the end of the study is agreeable to the sponsor.

- During the initiation visit the Investigator or delegate (for investigator initiated study) and monitor/CRA (for sponsor study) will provide a protocol-specific training session to all the members of the research team who will be involved in the research study.
- The investigator or monitor/CRA will ensure that the attendance sheets and other documentation are completed.

b. The protocol-specific training session will include, but is not limited to, the following:

- Aim and Objective of the protocol
- Time and events schedule for the protocol
- Subject recruitment
- Obtaining informed consent
- Procedure for dispensing the IP
- IP storage and records
- Protocol-specific forms and procedures
- Source documentation
- Adverse event reporting
- Additional information from the Investigator's Meeting (IM)
- Any other relevant information

c. The Investigator, monitor/CRA and CTC will:

- Develop a recruitment plan for subjects
- Identify a back-up to the primary CTC

➢ Study Activation and Initiation Visit Follow-Up

a. In preparation for study activation

- Confirm that the sponsor sends a written summary of key discussions and agreements made during the site initiation visit. Follow-up if necessary.
- Confirm readiness of the site to start the study.
- Confirm the receipt of all study-related materials such as CRFs, laboratory supplies, investigational product(s).
- Distribute protocol summaries and worksheets, if not done previously (the sponsor may provide study-related worksheets, however the site can prepare one).
- Notify all appropriate departments that the study is ready to enrol participants.
- Initiate study recruitment strategies and begin enrolling study patients/participants.

➢ Study conduct

a. Once the site is activated and starts recruiting patients, the Investigator and CTC will ensure the following:

- All study activities are accomplished according to the protocol and applicable regulatory regulations.
- Subjects sign the correct version of the consent form before any study-related procedures are accomplished.
- Medical History along with physical examination and Vital signs will be captured by Principal Investigator and Sub investigator after voluntarily signing of ICF by patient
- Data collected in the Case Report Form (CRF) are supported by source documents.
- Protocol deviations/non-compliance/violations/waivers if any should be notified to the SVIEC (Refer SOP for SVIEC communication) and the same must be documented in the source documents and appropriate CRF.

- Adverse events are reflected in the source documents and captured in the CRF.
- Serious Adverse events (SAEs) are reported to the Sponsor/CRO and SEC within specified time frame (refer SOP for SAE reporting).
- SUSAR and CIOMS should be notified in the timely manner to the SVIEC.
- The IP is being dispensed correctly and IP accountability records are being maintained.

b. While the study is ongoing, the CTC will ensure the following:

- The Sponsor/CRO is informed of all significant study events and staff members are documenting critical interactions with the Sponsor/CRO.
- Biological samples are being obtained, handled, stored, and shipped appropriately.
- Study supplies remain adequate.
- Study records remain confidential.
- All equipment is calibrated regularly and maintenance records are being kept.

➢ Premature Termination or Suspension of a Study

a. If the research study is prematurely terminated or suspended for any reason, the investigator/institution should:

- Immediately inform the SVIEC regarding the premature termination of the study in the format specified in the SVIEC SOP.
- Promptly inform the trial participants and include, where appropriate, the reason for suspension / early termination of the study.
- Assure appropriate therapy and follow-up for the participants, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority (ies).

- The PI should maintain documents as specified in the TMF list and take measures to prevent accidental or premature destruction

In addition:

b. If the PI terminates or suspends a research study without prior agreement of the sponsor, the PI should:

- Promptly inform the sponsor and the SVIEC regarding the termination.
- Provide the sponsor and the SVIEC with a detailed written explanation of the termination or suspension.

c. If the sponsor terminates or suspends a research study, the PI should:

- In case the sponsor chooses to or is required to terminate prematurely or suspend the research study, then the sponsor should notify the investigator(s), institution(s), the ethics committee and the regulatory authorities accordingly. The notification should document the reason(s) for the termination or suspension by the sponsor or by the investigator / institution.

Site close-out

a. Preparing the site for study close-out visits

- After the last patient has completed all scheduled visits associated with the study, arrange a mutually convenient date and time with the monitor/CRA to conduct the study close-out visit.
- Request the monitor/CRA for the visit agenda so key research personnel such as PI, Co I, CTC, research nurse and other team members will be available, as appropriate.
- Ensure all regulatory documentation and case report forms (CRFs) not previously monitored are complete and available for review.
- Ensure all data queries received to date have been resolved.

- Inventory IPs supply and complete final accountability records. If previously instructed to return or destroy IP, assure all required documentation is filed in the appropriate TMF for monitor/CRA review.
- Arrange monitor/CRA meeting with the PI and/or Co I and CTC to discuss any outstanding issues.
- PI will ensure that all outstanding payments are cleared as per CTA.

b. Managing the study close-out visit

- Ensure all documentation (e.g., regulatory correspondence) is filed appropriately and ready for the monitor/CRA to review during the close-out visit.
- Discuss all open study-related issues and what steps will be taken to resolve them in order to satisfy the sponsor/CRO requirement(s).
- Review with the monitor/CRA the list of outstanding issues related to regulatory documents, source data verification, IP reconciliation, and any requirements for data retention and storage.
- Discuss any concerns regarding the possibility of a quality assurance audit and/or inspection by SVIEC or external regulatory bodies. Include the CTC as appropriate.
- If the study involved electronic data capture, determine when hard copies/CD of all CRFs will be provided to TMC, if applicable.
- The PI is responsible for ensuring the appropriate follow-up, per the protocol, for any participant experiencing an ongoing unanticipated problem (e.g., serious adverse event) at study end and providing this information to the sponsor/CRO, assuring all requirements have been met.
- Arrange meeting of the PI and monitor/CRA to discuss any future considerations(e.g., publication of study data or future studies).

c. Follow-up after the study close-out visit

- For any remaining IP(s), ensure the item(s) is returned to the sponsor/CRO per their requirements.
- If the randomization code for any IP was broken for any reason, ensure complete documentation has been filed.
- Ensure return or destruction of all other study-related materials, such as unused lab kits and CRFs.
- Ensure any equipment on loan from the sponsor is returned or if mutually agreed by both the parties can be retained at the site.
- After all data queries have been resolved, check TMF, subject files and other study files for completeness.
- Arrange for transfer of study documents to secure storage.
- Submit the Final Closure Report to the SVIEC, in accordance with SVIEC SOP for Study Completion or Closure.
- Verify participant reimbursement or compensation if any have been distributed per the study budget, as outlined in the Informed Consent and CTA.
- If the informed consent and CTA, protocol or contract state subjects will be informed of their treatment arm, ascertain from the sponsor how and when this will be completed.

➢ Applicable Staff

This SOP applies to all the personals of the clinical research team and others who may be responsible for site initiation, activation, conduct and close-out at TMC.

These include the following:

- Investigator

- Research Team
- CTC
- Research Nurse
- Support staff

➢ Study Team Training and Study Handover

❖ Purpose

This SOP defines the procedure and recommendation of training of study team members and adequate handover to CTC/study team member, to ensure that the patient safety, protocol compliance, data integrity and overall quality assurance at the investigational site is protected and integrated as per the applicable regulations and guidelines.

Study team member must understand the responsibilities of the trials conducted at site and be appropriately qualified by education, training and/or experience to perform his or her research-related task(s). Some training may be obtained through internal hospital accepted training and certification program(s) or through external hospital accepted training and certification program(s).

The purpose of a handover is to ensure continuity of operations when the study team member, usually responsible, is not available due to temporary or permanent absence. A handover can be supported by a discussion to explain the status of the tasks, a summary of the work status in an email/ memorandum or, a more detailed file.

❖ Scope

This SOP will apply to all study team members conducting studies in SITE.

❖ Procedure

Study Team Training

- On appointment, all study team members will be given an appropriate study depending on the job specification to possess the right experience and qualifications and further training may be provided to bring them up to the required level for specific tasks. Duty delegation /job responsibility document will be given to every Clinical Trial Coordinator (CTC)/ team member.
- The Investigators, CTC and other study team members must undergo training which will enable them to understand their responsibilities, applicable regulations, guidelines and research studies and training should be documented in the training log.
- Each Investigator, CTC and study team members will review and learn the site's SOPs. It is recommended that SOP training must be included in the orientation of new clinical research personnel. All applicable clinical research personnel should be knowledgeable of new or revised SOPs.
- Good Clinical Practice (GCP) is a universal standard in clinical research that must be followed in every research protocol. GCP training and education are recommended for research team members, especially the Investigator and CTC. However, any member of the research team with a significant role in the conduct of a research study must be knowledgeable in GCP. All members of the clinical research team should GCP trained and certified.
- If scheduled, PI and CTC will attend the Investigator Meeting (organized by Sponsor) and complete all required training for a study. If PI is unable to attend the meeting, PI can recommend other study team member(s) to attend the IM. PI should be informed regarding the study contents discussed in IM.

- Before study initiation Sponsor/CRO will organize SIV meeting at site to train all study team members and all study team members should attend the meeting for thorough understanding of the study.
- PI and study team member(s) should be prepared to demonstrate all training received.
- CVs, GCP and other training certificates should be updated as required. It is recommended that an assessment of the employee's knowledge of the regulations and guidelines can be conducted upon recruiting 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 study.

❖ Study Handover

If any study team member is planning for leave or to resign, he/she must ensure that the proper handover is given to concern person identified by the PI, the identified person should be briefed in time before the person goes on leave to allow for any follow up questions.

Prior to leaving the study, the existing study team member should complete the following:

- Training on protocol and procedures e.g. SOPs and explanation of relevant documents
- Information regarding study subjects, study documents and all study related activities
- Outstanding data entry and/or data queries
- Training to complete source documents
- Explanation on the objectives & priorities
- Notification to the sponsor of the study team changes

- Notification to the active subjects of the study team changes if the research team contact information will change for the subjects.
- Provide a list of study-specific contacts (e.g., sponsor, monitor, vendors involved etc.)
- Provide a list of outstanding issues
- The leaving person has to make sure that the documentations concerned for the tasks is up to date and easily available, and if needed, revise it when preparing the handover.

If there is a change in PI, the following documents need to be revised and completed;

- Inform Sponsor and IEC regarding the change in PI in the Study team.
- Consider revising the protocol and informed consent form, as appropriate. Also consider notifying current subjects; correspondence sent to all subjects must be approved by the IEC, if applicable.
- Update the Form FDA 1572 or the Investigator Agreements, Investigator Undertaking and other required forms
- Update the Duty Delegation log
- Ensure that the new PI has completed the SOP required training and study-specific training. Written hand over should be given in order to ensure the continuity of work. The format can be a briefing note, a check list, or a schedule prepared to give all information.

When the study member returns from leave a hand over should be prepared to give updates on the status of the tasks.

The existing and new study team member should document the study handover in a note to file or other documentation in the TMF. The note should contain some of the items

above and the date of the handover. The new study team member should obtain documented study-specific training and any required approvals prior to being added to the duty delegation log.

❖ Applicable Staff

This SOP applies to all the existing personals of the clinical research team and any new member appointed who may be responsible for training and study handover as mentioned in this SOP(as per the delegation log).

These include the following:

- Investigator
- Research Team (listed in the delegation log)
- CTC