Effects of Advanced Trauma Life Support® on Adult Trauma Patient Outcomes (ADVANCE TRAUMA)

**MONITORING PLAN**

The George Institute for Global Health

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| **Completed by:** | | | |
| Author | *Name*  Dr. Samriddhi Ranjan | *Signature* | *Date* |
| **Reviewed by:** | | | |
| Co- Investigator | *Name*  Dr. Abhinav Bassi | *Signature* | *Date* |
| **Approved by:** | | | |
| Lead Principal Investigator | *Name*  Dr Martin Gerdin Wärnberg | *Signature* | *Date* |

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| --- | --- | --- | --- | --- |
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# Abbreviations

|  |  |
| --- | --- |
| **Abbreviation** | **Definition** |
| ATLS | Advance Trauma Life Support |
| COV | Close-out Visit |
| CRA | Clinical Research Associate |
| CRF/eCRF | Case Report Form/electronic CRF |
| REDCap | Electronic data capture system – database used for this study |
| IEC | Institutional Ethics Committee |
| ICH-GCP | International Conference on Harmonisation- Good Clinical Practice |
| ISF | Investigator Site File |
| KI | Karolinska Institutet |
| MVR | Monitoring Visit Report |
| PD | Protocol Deviation |
| PI | Principal Investigator |
| PISCF | Participant Information Sheet & Consent Form |
| PM | Project Manager |
| PV | Protocol Violation |
| SDV | Source Data Verification |
| SDMC | Trial Steering and Data Monitoring Committee |
| SOP | Standard Operating Procedure |
| TGI | The George Institute for Global Health |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TT | Trial Team |
| EOS | End of Study |

# Definition of Patient Status

|  |  |
| --- | --- |
| **Patient Status** | **Definition** |
| Screened | A participant who has met the eligibility criteria and *assigned screening number.* |
| Enrolled | A participant who has signed the ICD and met the inclusion/exclusion criteria and allocated *participant ID*. |
| Completed | A participant who will complete all the process till EOS. |
| Withdrawn | A participant who has enrolled but withdrawn due to:   1. Consent withdrawn by the participant due to any reason or without providing any reason for withdrawing consent. 2. Study termination by sponsor/IEC. 3. Investigator’s discretion. |
| Follow-up | A participant who has discharged and is in the follow-up phase of the study. |
| Lost to Follow-Up | A participant will be considered in Lost to Follow-Up category if:   1. If no contact has been established with participant by the time. 2. Insufficient information to determine the participant’s status on end of study (EOS). |

# Document Locations in Trial Master File

|  |  |
| --- | --- |
| **Document** | **File Path** |
| Data Management Plan |  |
|
| Database User Guide |  |
| Monitoring Visit Report Template |  |
|
| Essential Document Checklist |  |

# Introduction

The Monitoring Plan has been developed for verification of investigational site compliance with the protocol, data quality, accuracy and in compliance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines and ICMR biomedical guidelines 2017.

The completed and approved version of this Monitoring Plan and all approved revisions will be filed in the Trial Master File (TMF) and will be provided to the project team and monitors.

TGI will oversee and coordinate the conduct of the clinical trial. Monitoring will be conducted by TGI at all sites in India. TGI will use this plan as a guideline for:

* Overall site management
* Site visit preparation, conduct, and follow-up.
* Site monitoring and monitoring visit report (MVR)
* Completion timelines
* Safety reporting
* Training requirements
* Escalation of issues to the Trial Management Group

# Data Collection

The electronic data capture system is REDCap and can be accessed using the following link:

For complete details on data collection and the electronic data capture system, refer to ATLS Data Management Plan.

# Site Staff Training

Site staff will be trained for study protocol, basic level of trauma training, data collections over the electronic EDC. New site staff will be trained throughout the trial as required. Along with this the site staff will need to undergo GCP training. All team members listed on the site Duty Delegation Log (Appendix) will be required to undergo training on the protocol and trial processes. Besides this site CRC is also required to attend a ATLS observer-ship training. PI’s will be responsible to ensure all staff are qualified and undergo the appropriate training to perform the tasks they are delegated. Evidence of the training needs to be documented in training log (Appendix) or training certificates to be provided in case of GCP training and completion of a database access form (Appendix).

# Responsibilities of TGI Project Team

* **Protocol adherence-**CRA and PM will review protocol adherence, compliance with study procedure, ethical standards, and regulatory adherence.
* **Ongoing review of study progress** – progress of the study will be continually reviewed during weekly meetings with the site to ensure study deliverables are met. This will also include assess cluster performance in participant enrollment and track loss to follow-up rates, adverse reporting.
* **Review and maintenance of essential documents** – a comprehensive file review should be conducted **every 6 months** by the responsible CRA.
* **Data Management**-as the data custodians, central review of data will be undertaken. Data checks will be performed by the data management team as part of data cleaning throughout the study to ensure data integrity is maintained.
* **Management of safety information** – tracking the reporting of the safety events will be the responsibility of the CRA and PM.

# Monitoring Overview

Monitoring visit will be conducted at each site to assess the sites have a better understanding of the protocol and study procedures, and any study related requirements to be reinforced in person if necessary. Monitoring will be conducted by a designated Clinical Research Associate (CRA). There will be both on-site and remote (off-site) activities. There will be a focus towards central monitoring due to limited on-site monitoring. Remote monitoring activities may complement both central and on-site monitoring. Each monitoring activity will be undertaken to actively address the trial’s key objectives, maximize the quality and safety elements of the trial and minimize recurrence of any identified issues.

It is anticipated that each site will adhere to the following type and frequency for site visits:

|  |  |  |  |
| --- | --- | --- | --- |
| **S.no** | **Type of visit** | **Mode of Conduct** | **Frequency** |
|  | Site initiation visit | Remote | At the beginning of study batch |
|  | Interim monitoring visit (Remote/ onsite) | Remote /Onsite | Remote: Weekly for each cluster  Onsite: At the beginning of the study enrolment |
|  | Close out visit (COV) | Onsite | At the close of study batch |

The TGI team will follow all applicable SOPs regarding the conduct of monitoring visits, as well as the corresponding TGI visit report templates. Besides this the monitor to take care of following points in the monitoring:

### Critical Finding

Critical findings include protocol violations or serious breaches of the protocol, GCP or regulatory requirements. In the majority of cases, critical findings are those that impact, or potentially could impact, directly on the safety or rights of trial participants, or create serious doubt in the accuracy or credibility of trial data. Examples include, but are not limited to:

* Any major finding that does not improve, or repeatedly recurs.
* Investigator or site staff backdated/altered the dates of participant signatures on consent forms.
* Written consent not obtained for an enrolled participant.
* Participant enrolled in the study, but not meeting eligibility criteria.
* Participant screened or enrolled into trial before ethical approval was obtained.
* Any safety reporting not done as per the required reporting procedures.

### Major Finding

Major findings include deviations from the protocol that may result in questionable data being obtained or errors that consist of a number of minor deviations from regulations, suggesting that procedures are not being followed. Any major finding that is not corrected, or that recurs after initial notification, will be raised to critical status. Examples include, but are not limited to:

* Consent forms not locatable at the time of monitoring.
* Failure to assess safety reports according to the protocol.
* Recurrent missing documentation; and
* Frequent data inaccuracies.

### Other Finding

Other findings are errors or deviations from procedures that do not have an important impact on the data that are collected, or do not affect the safety or rights of participants. Examples include but are not limited to:

* Not signing and dating changes
* Single instances of missing documentation; and
* Single instances of data inaccuracy.

### Corrective and Preventative Action (CAPA)

A CAPA is a documented process of improvement to identify and eliminate the root cause(s) of the protocol deviation or other non-conformity, and thus prevent their recurrence. It is required to appropriately address risks in each PV filed where the issue is serious or repetitive and systemic. CAPAs will be filled for all protocol violation in the PD/PV log (Appendix).

### Filenames

Filenames to follow the ATLS naming convention: ‘Project name>Document name>Version number>Version date’.

### Trial Master File (TMF)

TMF will be established at the beginning of the trial and contains all essential documents held by the trial sponsor, The George Institute for Global Health (TGI), to comply with ICH GCP requirements. The establishment and maintenance of the TMF is the responsibility of the Project Manager with assistance from the Clinical Trial Associate. The TMF will be reviewed **every six months** to ensure that the contents are current and complete. The TMF is held electronically at: <https://georgeinstitute.sharepoint.com/:f:/s/TGIATLSKIStudy/ErnMzrrEuTdCnMwoTIYljJAB-9T3snKK7j2HxjTPS1tH1A?e=b5BdTW>

### Investigator Site File (ISF)

ISF will be established at the beginning of the trial and contains all essential documents held by the trial sponsor, The George Institute for Global Health (TGI), to comply with ICH GCP requirements. Maintenance of ISF will be responsibility of the sites CRC. ISF will be reviewed at the time of onsite monitoring and at the close out. Besides this it will be reviewed during remote monitoring **at every 6 months** to ensure that the contents are current and complete. ISF will be made electronically.

## Site Initiation Visit and Activation

A remote site Initiation Visit (SIV) will be conducted for all site staff. The SIV will include information on roles and responsibilities, study rationale, overview of study procedures and data base training. The Site Initiation and Activation Checklist (Appendix) will assist the Monitor. A ‘green light’ process using the checklist is to be implemented to ensure that sites do not begin trial recruitment until all initiation and activation activities have been completed. Slides and materials from the SIV will be provided to the site. If no participants have been screened within 1 month of initiation the site. TGI will be responsible to send an email to trial management group (TMG). The TMG will discuss the continuation of site and discuss opportunities to enhance recruitment.

### Conducting a SIV

The PM along with the trial team will decide a day and time for the conduct of SIV as mutually agreed upon by all the site PI. SIV will be conducted remotely. Topics to be covered during the initiation visit are listed on the agenda and the slide-deck of the SIV master slides (Appendix). All topics specified on the agenda and in the SIV master slides must be included. The SIV materials are to be developed by the TGI-PM and by the lead investigator at India and at KI.

### Report Requirements for SIV

The Site Initiation Visit Report (Appendix) documents the activities that were reviewed and discussed during the SIV. The report should include any action items or issues that require follow up from the site.

The monitor should complete the **SIV report within 7 working days** after the conclusion of the SIV and the report finalized within **10 working days** of the conclusion of the SIV. The SIV report from each batch to be reviewed and signed off by the PM.

The SIV Report and follow up letter outlining the activities during the SIV and any pending action items required from either party are to be sent to site within **10 working days of the SIV**. The monitor should follow-up on any action items or issues until they are actioned or resolved. A copy of the SIV Report must be filed in the ISF and TMF along with the Training Log (Appendix) documenting staff attendance at the SIV.

### Confirming Site Activation

Once the Site Initiation and Activation Checklist has been signed-off and there is a ‘greenlight’ for site activation, the PM must formally notify the site via email that they have been activated and can begin recruitment.

## Remote Monitoring

### Frequency of Monitoring

Remote (off-site) monitoring visits will be conducted for all sites on a for **1-2 hours on weekly basis** for each site. The monitor will set a convenient time for remote monitoring with individual sites and share the meeting link. Extensive monitoring can be done with increase in frequency, if there are data quality concerns.

### Monitoring Visit Procedure

Remote monitoring activities include review of site enrollment status, data collection, reporting of safety events, tracking the recording of PD and PVs. The following items will be covered in each of the remote monitoring visit.

|  |  |
| --- | --- |
| Recruitment rate | Review of current recruitment rate and participant status to ensure rate is in line with expectations and all participants in the database are assigned the correct status |
| Screening and Eligibility | * Date of screening to be prior to consenting * Screening and enrollment updates as per the logs |
| Consenting | * Date and time at which consenting was done (including consent wavier, opt-in consent, assent) and date and time of opt out consent * LAR details * Consent is withdrawn, if applicable |
| All forms (Baseline, Prehospital. ATLS adherence form, Emergency Department, Hospital, Surgery, Imaging, Transfusion, Injury, Individual Mortality Status, Quality of Life, Disability (WHODAS 2.0), Return to Work, End of Study | * Check all items have been entered for each form, raise a query for any missing items to identify. * When participant has completed the study, check that the end of study form is completed. * Completion of follow-up forms at 7th day, 30th day, 90th day * Check outstanding queries have been addressed and if any can be closed. * Check site to enter the data promptly within 3-4 working days |
| Safety Events | * The type of event recorded in the CRF. * PI to assess the safety event andto report the event to TMG within 24 hours * Maintaining timelines for SDMC * Maintaining timelines for IEC |
| Participant retention | Check percentage of participants who have withdrawn consent for each site. |
| Protocol Deviations and Violations | * Check the deviation and violation log * Check protocol violations are reported withing timelines * Check CAPA’s are filed for reported PVs |
| Data trends | Check for multiple outlier values, poor variability or rounding tendency |

### Report Requirements

A summary of the queries raised during the central monitoring will be emailed to the site coordinators via email **within 2 days of remote monitoring** in an excel spreadsheet. It is expected that sites respond to these queries **within 1 week** of it being opened. Tracking of queries that remain open, is to be maintained in the site excel spreadsheet. All issues and action items must be followed-up until they are actioned or resolved. The monitor and site staff will discuss via subsequent remote monitoring visits or via email for queries which are pending or any other action items which are to be completed. The template for the email will contains following:

**Box-**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Dear <Site CRC>,*  *Sharing the monitoring query sheet <dated>with the summary of details below. Requesting you to respond to the queries before <date>.*   |  |  | | --- | --- | | ***Participant Status*** | ***Number*** | | *Participants ID reviewed* |  | | *Total participant enrolled* |  | | *Number of Queries pending from last visit* |  | | *Participant ID soft lock completed* |  | |

### Outstanding Action Items

The monitor will work with site staff to resolve any outstanding issues resulting from the remote monitoring detailed in the excel sheet, in a time **within 1 week.** It is recommended that all pending issues are to be closed **within 30 days** through discussions. In-case there are any withstanding issues found at the time of remote monitoring which cannot be resolved subsequently, then the same will be resolved at the time of on-site monitoring. Any remaining outstanding remote monitoring queries should be listed on the MVR at the completion of on- site monitoring visit. In case persistent issues are found in the data recording, training or re-training needs will be identified as required and will be conducted by the monitor or PM.

## On-site monitoring visit

Onsite visits will be done once **first 10 participants** are enrolled for each of the sites. Any systemic issues identified can be addressed in a face-to-face meeting with the investigator and other site staff. Monitoring date should be scheduled at a mutually convenient time for sites and the CRA/PM and should be confirmed in writing (email) with an outline of the activities planned for the visit. The frequency of on-site visits may be altered depending upon following:

• high recruiting site

• in case of poor site compliance

• in case of quality concerns

• in case of data entry delay or significant errors

### Scheduling & Preparation

The monitor will liaise with the site to schedule the visit on a mutually agreed date. The visit date should be set at **least 2 weeks in advance** to allow enough time for both the monitor and site staff to prepare. Remind the site to arrange a workspace for the monitor. The monitor will schedule monitoring visits and a confirmation email to be sent to investigational site staff **at least 2 business days** before visit, including date, time and place of the visit, access to investigational site staff (investigator, study coordinator) summary of the planned activities and document availability at site. A copy of the communication email to be filed in the site ISF. The monitor should meet with the Principal Investigator (PI) or other key investigators at each visit. The monitor must record the site attendees during the visit in the MVR and sign the site visit log (Appendix).

Prior to the visit, review the following:

* Source documents for screening and enrollment
* ISF to identify documents requiring collection
* Source documents for reported safety events
* Actions pending in remote monitoring visit (if any)
* Source documents pertaining to PD/ PV log

### Monitoring Visit Duration

Each monitoring visit should take an average of 8 hours. Monitoring visit will be guided by MVR template. Each item required to be checked as listed in the template. Additionally, another 8 hours will be required for preparation, travel, MVR completion, and follow-up communication. Sites requiring visits of longer duration, or co-monitoring visits, will be discussed with the PM prior to scheduling the visit.

### Process Monitoring

At the time of site monitoring the monitor need to conduct the process monitoring. The process monitoring will be done for the following procedure.

* Screening procedure
* Consenting procedure
* Enrollment procedure
* eCRF entry
* Follow-up procedure
* Review of collection of study procedures like Quality of Life, Disability (WHODAS 2.0), Return to Work, End of Study, Adherence form (if applicable)

### Discussion with PI and site staff

Meeting with the PI and other key site staff to discuss study status and recruitment at the end of the monitoring visit. All the monitoring observations will be discussed with the Site PI / designee. These findings will also be mentioned in the MVR. Any major issues such as PVs discovered during a site monitoring visit should be discussed directly with the PI and to be maintained in a PV log (Appendix). The site visit log must be signed by the monitoring team and countersigned by the site team.

### Report Requirements & Follow-up Activities

All queries raised during the monitoring visit will be documented in the MVR (Appendix). The monitor will document monitoring visit findings, including any questions or issues raised at the visit, and resulting action items in a monitoring visit report. For on-site queries in relation to source documentation, the study monitor is to keep record of what they believe the correct data entry should be. The study monitor can then close the query once the data has been amended. Unless the site advises the data is different to that which the monitor has documented, in these cases the query may stay opened or answered until clarified. The monitor must ensure that corrective and follow-up actions of monitoring are closed out in a timely manner.

The MVR will be completed by the monitor **within 7 business days** of the monitoring visit. Where more than one site has been monitored in the same week, all monitoring reports should be completed within **10 working days and finalized within 15 working days** of the visit. A formal Monitoring Visit Cover Letter will be provided to the site following site monitoring visit to confirm corrective and other follow-up actions. The letter will include details of what activities were conducted during the monitoring visit, all issues identified during the monitoring visit and the action required to resolve them. Corrective actions will be confirmed at the next monitoring visit. Monitor will also specify the number of informed consent documents reviewed along with the participant ID in the MVR. The MVR will be reviewed by the PM within a further **5 business days**. The cover letter and follow up letter will be emailed to the site **within 7 to 9 business days** of the visit. Issues relating to safety events or documentation will be discussed with the PM and addressed in the cover letter, as appropriate. All issues identified at the site monitoring visit should be followed until resolution. It is the responsibility of the sites to resolve all the queries in **10 business days**. A copy of the Monitoring Visit Intimation and Follow letters must be filed in the ISF.

All PVs and PDs must be documented in the MVR and summarized in the cover letter, along with action taken to prevent reoccurrence. Additionally, all PVs & PDs it to be recorded in the PD & PV logs. The MVR template includes a section to list the PVs and PDs as a reminder. Monitor to ensure that appropriate preventive action is implemented where needed. If issues cannot be resolved effectively then the monitor should escalate the issues to the PM to assist with resolution.

### Outstanding Action Items

The monitor will work with site staff to resolve any issues resulting from the monitoring visit and action any outstanding action items detailed in the Monitoring Visit Report, in a time span of **4 to 6 weeks** post visit. The monitor and site staff will discuss via subsequent remote monitoring visits or via email for all resolved, in process, and pending action items. All issues and action items must be followed-up until they are actioned or resolved. It is recommended that all issues are closed within **30 days.**

## Monitoring Visit Procedure

Montoring visit procedure will slightly vary for the remote and on-site monitoring activities. Table no will give a brief description of the activities which will be performed at the remote and onsite monitoring.

At each interim monitoring visit, the following must occur:

**Table:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Source Document** | **% of review** | **Remote**  **Monitoring** | **Onsite Monitoring** |
| Review of documents relevant to ethical approval | 100% | ✔ | ✔ |
| Eligibility, inclusion/exclusion criteria | 100% | ✔ | ✔ |
| Informed consent forms | 100% | ✔ | ✔ |
| Paper CRF, medical records, patient notes, hospital admission and discharge summary/ referrals and questionnaires for all screened patients | 30% | ✔ | ✔ |
| All reported safety events | 100% | ✔ | ✔ |
| PD/PV reporting | 100% | ✔ | ✔ |
| Review of ISF | 100% | ✔ | ✔ |

### Participant Screening and Enrolment Rates

A 100% review of all the participants who were screened along with the medical/ hospital records will be done during the interim monitoring visits by monitor during the regular remote or scheduled on-site monitoring. Sites can scan the document and present the required document to the monitor. It is the duty for the monitors to check for:

* Review of eligibility-All participants must fulfil the eligibility criteria at the time of enrolment. Confirm all required data have been entered to assess eligibility through source notes
* Check all inclusion and exclusion criteria
* Check screening and enrollment log (Appendix)

Besides this, the sites will need to update the participant screening and enrollment rates on a **weekly manner** in Screening & enrolment log (Appendix) during weekly remote monitoring. If the participant enrollment is less than 12 participants for 3 consecutive months. TGI will be responsible to send an email to trial management group (TMG). The TMG will discuss the continuation of site and discuss opportunities to enhance recruitment.

### Review of informed consent forms

100% percent review of all the paper-based consent form recoded, this will include wavier of consent (if recorded), opt-in and opt out consent (if recorded). Each participant’s original signed participant Information Sheet and Consent Form (ICD) to be reviewed both in the paper records and tally with the information recorded in database, **on weekly basis**. Sites are required to scan paper-based consent forms, masking the identity of the participant and project at the time of remote monitoring.

The monitor will conduct the following checks:

* All fields have been completed appropriately.
* Verify that all participants have signed and dated the correct version of the consent form.
* The Duties Delegation Log to be updated for the responsibility for obtaining informed consent at site.
* Ensure study team members, staff member reporting to the study investigators, hospital staff who are on direct payroll of the site, are not signed as an impartial witness to an illiterate participant.
* Legally Acceptable Representative (LAR) was present during the informed consent process. The LAR can be a first or second-degree blood relative, or an individual authorized by the court.
* If the said LAR is illiterate, and cannot read and sign the ICF, then signatures of an impartial witness will be sought. For illiterate participants/ LAR right thumb impression to taken. The date of the witness signature should be on the same date as the participant signature.
* The monitor will also be required to report any protocol deviations identified for the consent procedures.

### Monitoring of eCRF data

A 100% remote monitoring will be conducted on the eCRF on the web-based database (REDCap) for all the sites by the monitor. Weekly review of eCRF entries will be performed by the monitors. A 30% review of the paper based CRF will be done at every **three months** through remote monitoring. Sites are required to fill eCRF in a timely manner **within 3-4 days** of data collection with a steady and reliable flow. The database will be checked to ensure data integrity, correctness, completeness and consistency of the entered data. A summary of the queries raised will be emailed to the site coordinators as per the Box

### Review of Safety event reports

This trial will not collect adverse events or serious adverse events. Only the enlisted events will be documented as safety events. Any other safety events that are identified by the clinical research coordinators or local investigators during the trial will also be reported. This may include missed injuries or missed investigations, which could be suspected if certain injuries or investigations are identified during the intervention phase.

The safety events will include following:

* There is a life-threatening condition
* Prolong hospitalization
* Result in meaningful harm to the participant
* Prolonged mechanical ventilation (> 7 days)
* Initiation of renal replacement therapy
* Prolonged (> 2 days) or renewed (restart after at least 2 days without) use of Vasopressors such as norepinephrine or vasopressin

A 100% percent review of safety events to be reported. All safety events will be recorded in the Case Record Form (CRF). It will be the responsibility of the PI assess the safety event andto report the event to **TMG within 24 hours** of its occurrence by the site via email. The recorded CRF will be shared with the TMG via email (Appendix-CRF) by site PI. The TMG will then assess if the event can be considered related to the trial or the intervention **within 24 hours** of it being reported. Events that are considered probably related will be reported immediately to the Trial Steering and Data Monitoring Committee (SDMC) via email **within 5 working days** via an email. Along with this it is the responsibility of the respective site to inform their IEC as per the requirements by the ethics.

### Review of Protocol deviations (PDs) and protocol violations (PVs)

A protocol deviation is any non-compliance or excursion from the ethically approved trial protocol, including any deviations that are enacted intentionally for the direct purpose of maintaining the safety of the trial participant. Protocol deviations and violations to be recorded whenever identified during trial.

Monitors are expected to review all the violations or deviations recorded at the sites in the PD and PV log (Appendix) and in the clinical trial report (Appendix). A 100% review of the PD/PV will be done during each visit. Minor protocol deviations do not require reporting and will be captured in the PD/PV log. All PV must be taken seriously, and corrective action must be implemented as soon as possible to prevent recurrence. In case of PV the site is expected to document corrective and preventive actions (CAPA) in the PD/PV log (Appendix). CAPAs will aims to resolve compliance issues and to prevent any further recurrences. Any major issues such as PVs and PDs discovered during on-site monitoring visit should be discussed with PM upon return to the office. Following enlisted items will be considered as PD or PV:

|  |  |
| --- | --- |
| Protocol Deviations | * Missed follow-ups * Missed recording of the assessments and CRF’s * Recording of data beyond the scheduled timelines * Decisions on how to allocate hospitals to batches based on other considerations than those specified in the protocol |
| Protocol Violations | * scheduled ATLS training were not given to the doctors * delay in the transition of one phase to another * or a cluster fail to stick to the allocated timelines. |

It is the responsibility of the PI to report to monitors, without delay any serious breaches such as deviations and violations from the trial protocol, ICH-GCP and other regulations. The PI to inform about PVs to monitors via email within **2 days of identification** and to their local IEC. It is recommended that all issues are closed within **15 days of discovery**.

### Monitoring Logs

Copies of the following logs and documents will be requested and reviewed by trial monitors on a regular basis.

* + Delegation of Duties Log
  + Training Log
  + Protocol deviations and Violation log

### Review of Participant Files:

A random 30% of enrolled participants will be selected for SDV this could be done at 3 months through remote. Monitors will conduct source data verification (SDV) of these records and will also cross-check the data entered in the electronic database. Participant files to be reviewed for the following:

1. Recorded paper based CRF
2. Review of medical records
3. Participant admission and discharge summary/ referrals

SDV of the above documents will be done during both remote monitoring and onsite visit. A 30% of SDV will be done for participants which will include completed/ ongoing participants in both intervention and control group. SDV can be done after **every 3 months** through remote or onsite monitoring whichever is scheduled. Sites are required to scan paper-based documents, masking the identity of the participant and project at the time of remote monitoring. Records that will be assessed are medical records, patient notes, any other hospital records. These participants will be selected randomly will be checked for following:

* The selected participants will identify by the PM. It will be the responsibility of the PM to share the list of selected participants to CRA, prior to the monitoring visit.
* If more than 30% of data entry errors are found the monitor should review an additional 10% of participant source notes, where time allows.
* In case, many errors were found then following will be applicable:
* If a large number of errors (>5%) are identified in the 30% random sample, then a further 10% random sample needs to be monitored.
* If again a large number of errors (>5%) are identified, then 100% of the participants will need to be monitored and outcomes need to be discussed with the site PI and further training of site staff conducted.

### Review of ISF/ Other documents

Each site will be provided with all the appropriate documents, logs, templates for the compilation of an ISF. Sites must ensure that these documents are updated in the ISF. Prior to a site being activated and throughout the lifecycle of the trial, sites to maintain all essential documents in the ISF, and file updates as required. Superseded and current versions are to be filed. Where training is provided to site staff via a slide deck or other material, the content will be appropriately filed within the site’s ISF for ongoing and future reference. During remote monitoring visits, the monitor will review the ISF for accuracy and completeness. ISF review can be done **6 monthly**. Review of the following documents will be done for each of the onsite monitoring visit.

* Review correspondence with site, and missing essential documents
* Review of all outstanding issues for follow-up and completion
* All logs (duty delegation log, training logs, site visit log (Appendix).
* Review project status and tracking information, including recruitment, data collection (entered data, missing data, open queries etc.).
* Verifying the qualifications and training of all site staff including any new staff to ensure they are adequate, including collection of curricula vitae and ICH-GCP certificates as required. Also, identifying any required training and support to investigational site staff.
* Review all the documents pertaining to ethics submissions including the amendments filed and reports submitted to ethics during the onsite visit. In case any subsequent submissions are done for the ethics monitor can review the documents during the remote monitoring.

The monitor will alert site staff to:

* Update or/ any discrepancies in the ISF.
* Upcoming submission dates for reporting, for example annual progress report or annual safety reports.

### Project Dashboard

Data that sites enter in the REDCap database is integrated with project dashboard. The Project Dashboard can also display data trends (range, variability) within and between sites. By monitoring eCRFs, the Project Dashboard, the monitor is alerted to situations that need investigation. Project Dashboard will provide a comprehensive overview of accumulating data and performance metrics relating to:

* Participant screening and enrollment
* Monitoring
* Safety reports
* Follow-ups

## Site Close-Out Visit (COV)

All sites that were initiated in batch will receive an onsite COV. The purpose of the COV is to resolve any outstanding queries/issues, review the investigator requirements including document maintenance and storage with the PI.

### Pre-Requisites

Site closure should occur when all participants at the site have completed with all follow-ups, including reporting of all safety reports. Site closure may not be finalized until all data have been received and no queries are outstanding, and all the forms are locked by the monitors. Non-active sites will be closed out only with the approval from the Trial Management Group.

### Close-Out Activities

Site PI will receive a COV confirmation email at **least 2 business days** prior to the visit detailing what will occur at the COV. COVs must include all site staff with key responsibilities, including the PI or delegated co-investigator, study coordinator, or any other relevant staff. Prior to starting site closure, the monitor should:

* Identify outstanding queries
* Review previous MVRs and correspondence to identify outstanding issues
* Review the TMF to identify missing or incomplete essential documents
* Review financial status and final payments
* Collection of study device??

The monitor will complete the following:

* Perform final review of eCRF and queries to confirm that all data has been collected including PI sign-off of eCRFs for the designated forms (Screening form, consent form consent withdrawn, baseline, ATLS adherence, surgery, and mortality form).
* Confirm that all other outstanding monitoring issues have been resolved
* Review all safety reports to ensure that reporting according to the study protocol has been completed

• If applicable, confirm that all audit findings have been appropriately closed out

• Review ISF to confirm that all applicable documents are present. Collect any missing documents for the TMF that relate to the domain including final copies of:

o Delegation of Duties Log

o Personnel Training Log

o Monitoring Log

During the site closure period the monitor is responsible for advising the investigator of the following ongoing obligations:

* Requirements for, and the importance of, study record retention by the investigator and other project-specific documents, participant identification numbers
* Arrangements for the final project payment, if applicable
* The publication and reporting plans as per protocol

It is the responsibility of the monitor to ensure that the site staff make necessary notifications of project completion or early termination and submit project summaries to TMF, if required.

### Report Requirement and follow-up

The monitor should complete the COV report within **5 business days of site closure**. The PM will review and approve the COV report within a further **5 business days**. Follow-up any actions arising from the COV is to be completed in **5 business days after receiving** the report. When all site closure activities are complete, a Site Closure Confirmation letter (Appendix) will be sent to the PI by the monitor. The monitor will file all site closure documents in the TMF in a timely manner.

### Monitoring reports timelines

|  |  |  |
| --- | --- | --- |
|  | **Monitor reporting timeline** | **Site response timeline** |
| SIV report | within 10 working days |  |
| Remote monitoring | within 2 working days | within 1 working week |
| Outstanding monitoring issues | within 1 working week | within 30 days |
| Onsite visit | within 7 working days | ?? |
| COV | within 5 working days | within 5 working days |

# Communication

Communication with sites will mainly be via email. Important email correspondence needs to be saved on the TMF under the site-specific folder titled “Site Communication”. The email needs to be saved with a short title regarding content and a date. All telephone contacts should be documented by confirming the discussions in a follow-up email.

# Trial Steering and Data Monitoring Committee

A Joint Trial Steering and Data Monitoring Committee (SDMC) will be designated for this study. The SDMC’s responsibility is to oversee the trial, review results of interim analyses and safety events reported by the TMG, and review trial data for each batch, assessing data quality, completeness, cluster performance in recruitment and loss to follow-up rates, and external factors affecting trial validity, safety, or ethics. This committee also offer guidance to the TMG. Frequency of this meeting will be after the completion of each batch. However, meetings can be more frequent if required.

# Reporting timelines

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reporting Event** | **Reporting authority** | **Reported to** | **Timeline for reporting** | **Response time** |
| Safety event reporting | PI | TMG | 24 hrs | 24 hrs-TMG |
| Safety event reporting | PI | IEC | ?? | Not required? |
| Safety event reporting | TMG | SDMC | 5 days | ?? |
| PV | PI | Monitor | 2 days | For CAPA? |

# Trial organization team meeting timelines

|  |  |  |  |
| --- | --- | --- | --- |
| **Trial organization team** | **Frequency** | **Documents to submit** | **Timelines** |
| Trial Team Meeting | Weekly/ biweekly | Meeting Minutes | 7 days after the meeting |
| Trial Management Group (TMG) | Monthly to every 6 months | TMG/ SDMC report template | Within 1 week of the meeting |
| Trial Steering and  Data Monitoring Committee (SDMC) | After the completion of each batch | TMG/ SDMC report template | Within 1 week of the meeting |
| Remote Monitoring | Weekly | Query Sheet (in excel) | Weekly |