

Monitoring Plan
Version and Date
Trial Code:

<trial code>

<trial title>

Monitoring Plan

Trial Sponsor:

Study Coordinator:

Version:

Date of Release:

Project Manager:

Revision History

Date	Version Number	Revision Summary (describe reasons for the change and the sections impacted)
	1.0	Original Version

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1 LIST OF ABBREVIATIONS

ABBREVIATIONS	TERM
AE	Adverse Event
COC	Clinical Operations Coordinator
COV	Closing Out Visit
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
CTC	Clinical Trial Coordinator
CV	Curriculum Vitae
DM	Data Manager
EC	Ethical Committee
FROM – E.T.S.	FROM-Fondazione per la Ricerca Ospedale di Bergamo – Ente del Terzo Settore
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
PI	Principal Investigator
PM	Project Manager
PSV	Pre-Study Visit
QAM	Quality Assurance Manager
RMV	Routine Monitoring Visit
TMF	Trial Master File
SAE	Serious Adverse Event
SDV	Source Data Verification
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
TMF	Trial Master File

2 INTRODUCTION

The Monitoring Plan describes the monitoring procedures established by the Sponsor for a specific study to guarantee compliance with the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guideline (§ 5.18.1) and applicable regulatory requirements, which require Clinical Research Associates (CRAs) to verify that:

- The rights and well-being of human subjects are protected.
- Reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirements.

This monitoring plan will be implemented in conjunction with the FROM – E.T.S. SOP CLI04 – Monitoring.

This document describes the trial-specific monitoring activities and specifies the data to be reviewed over the course of the clinical trial. This monitoring plan will be followed to monitor the trial site approved to perform the clinical trial.

This Plan does not replace any information reported in the Clinical Trial Protocol/Amendments, but provides further details needed for a consistent conduction of monitoring activities.

The monitoring plan be updated periodically.

3 DETERMINATION OF EXTENT AND TYPE OF MONITORING

The extent and type of monitoring for the present trial have been determined on the basis of a risk evaluation taking into consideration elements such as study complexity, current knowledge of the IMP(s) effects, IMP(s) safety profile and phase of development, sites' expertise and experience in similar studies.

The risk evaluation has been performed with the aid of a pre-defined matrix including 16 items. A score corresponding to the estimated risk is assigned to each item (1=low; 2=medium; 3=high) and recommendations about type (on-site vs. remote) and extent of monitoring are derived from the total scores obtained.

The Monitoring Plan will be revised during the trial if the level of control and/or assistance provided to the sites turns out to be insufficient.

Circumstances for changes may include, but are not limited to:

- Accrual rate significantly lower or higher than expected,
- Quality issues (non-compliance),
- Complexity of the trial,
- Investigational Site problems requiring prompt action.

The changes will be recorded in the Revision History. The revised and approved version(s) of the Monitoring Plan are sent to all involved CRAs.

If site-specific exceptions to the present plan are to be made, these are to be documented with the relevant rationale in a Note to File.

4 RESPONSIBILITIES

The CRA is responsible for organizing, conducting and documenting monitoring site visits and any other significant contact with the study sites. The monitoring visit will be performed according with the SOP CLI04 Monitoring.

Any relevant issue and action taken must be duly documented. Significant protocol deviations and non-compliance with GCP, applicable SOPs and regulation must be immediately reported to the FROM – E.T.S. PM. Appropriate action will be discussed with the COC and the QAM and promptly implemented.

The CRA must ensure that all required regulatory approvals, essential documents, training, technical equipment and IMP supply are in place before the first patient is enrolled at a clinical site.

The PM is responsible for supervising the monitoring activities, reviewing and signing monitoring visit reports and for providing advice to CRAs concerning correct interpretation of the study protocol and management of any non-compliance.

To document the qualification of the trial site to perform the trial the CRA must collect the Site Signature and Delegation Log (T-CLI04-06) issued by the PI and the CV of the site personnel before the trial start. This documentation must be kept up-to-date during the trial conduct.

5 DELEGATION OF RESPONSIBILITIES

The monitoring activities for all sites involved in the trial will be carried out by personnel of the Sponsor and/or by designated by the Sponsor [i.e. clinical research organizations (CROs) or freelance CRA(s)] on the basis of the monitoring plan specific for the trial and under the terms and conditions reported in the relevant agreement.

The list of clinical sites assigned to each CRA is reported in the paragraph below Trial Team Contact Table.

6 COMMUNICATIONS

Each Monitoring Visit will be agreed with and communicated to the Investigational Site Staff by e-mail, and the Sponsor Project Manager will receive a copy of each communication.

Any issues related to monitoring activities should be discussed with the Sponsor Project Manager.

7 KEY MILESTONES

Expected number of patients (enrolled)	
Planned number of sites	
Planned First Patient In	
Planned Last Patient In	
Planned Last Patient Visit	
Frequency of follow up visits	

8 CRA TRAINING

Prior to performing monitoring activities, the involved CRAs will receive clinical trial- specific training. Training material (e.g., slides) will be filed in the Trial Master File (TMF) together with attendance lists and training certificates.

As needed, additional training may be planned and given. The Sponsor PM will be available for the CRAs for any further clarifications and training needs.

9 SITE STAFF TRAINING

Key site personnel (i.e. PI, Co-I, Data Manager) will be trained by the CRA during the Site Initiation Visit. All site attendees (as listed on the Site Signature and Delegation Log; T-CLI04-06) should be trained and sign the Site Staff Training Record (T-GEN-03-04) to document their understanding of the study procedures and requirements.

The PI/Co-I and Data Manager will be responsible for training all Co-Is, study nurses and other relevant personnel that are not present at the SIV. This training must be documented on the Site Staff Training Record (T-GEN-03-04).

All changes in the study team should be reported by the site staff to the CRA and then recorded on Site Signature and Delegation Log; T-CLI04-06). Training is provided by the CRA or appropriate site trial personnel to the new staff, duly documented on the Site Staff Training Record (T-GEN-03-04) and filed in the ISF.

The following training should be provided to site staff: therapeutic area, protocol, investigational product, Investigator’s Brochure/Reference Safety Information, vendor (including CRF, Central Lab, PK Lab, and IRB).

10 DATA FLOW

The clinical data will be collected through electronic Case Report Forms (e-CRF). The software used for clinical data management is <insert the name>. Prior to the SIV, the CRA will receive an account (username and password) to access the Clinical Trial database.

During the SIV the CRA will train the site personnel authorized to enter data in the eCRF and will provide them with the CRF Completion Guidelines.

Sponsor PM/DM will perform consistency checks on the clinical data entered in the Clinical Trial database and issue queries addressed to the site personnel through e-mail. The CRAs is responsible for verifying that queries are timely and properly solved and should assist the site personnel in queries resolution if needed. After site personnel data/query reviewing, CRA and/or Sponsor PM will verify data and close/update query.

Only Principal Investigator (PI) or Co-Investigators are allowed to sign the e-CRF.

In all cases, it remains responsibility of the PI to check that the e-CRF are completely and correctly filled in.

11 SITE MONITORING VISITS

Monitoring visits will be done to ensure adherence to the FROM – E.T.S. SOPs, the protocol and ICH-GCP. The monitoring activities are regulated by the FROM – E.T.S. SOP CLI04/1 Monitoring.

Monitoring is performed by visiting the clinical sites (‘on-site’ visits), by phone call and electronic documents exchange (‘remote’ visits).

11.1 Frequency and type of visits

The monitoring visits schedule has been based on the risk assessment documented in the TMF.

On the basis of the risk assessment results and further evaluation by the Sponsor PM the following monitoring schedule was established for the present trial:

Type of visit	On-site	Remote
Pre-study Visit		
Site Initiation Visit	<insert no. of visit>	<insert no. of visit>
Routine Monitoring Visits	<insert no. of visit>	<insert no. of visit>
Close Out Visit	<insert no. of visit>	<insert no. of visit>

The PM is responsible for planning the monitoring visits and regularly sharing the plan with the CRA.

Before each visit the CRA will contact the site personnel well in advance to schedule a suitable date and will send a visit agenda including activities to be performed, relevant time schedule and site staff involved.

The procedures described in the following sections are to be intended as a general guide and provide a standard for the minimum level of control foreseen for the present trial. However, monitoring activities can be increased and adjusted based on the findings and upon agreement between the CRA and the Sponsor PM.

11.2 Pre-study Visit

The PSV is to be performed after a clinical site potentially suitable for trial participation has been identified. It is essentially aimed at verifying the feasibility of the study at that specific site, specifically the availability of the study population and of any study-specific equipment, specialized personnel, logistic requirements.

If a Qualification Visit (SOP CLI04 - Monitoring) has been already performed at the site, a pre-study visit focused only on protocol and trial procedures is carried out at the time of each new trial.

In addition, during the Pre-Study Visit a clear feed-back should be obtained from the Investigator about his/her interest and commitment to participate.

The results of the visit must be documented in the Pre-Study Visit Report and if the outcome is positive, the CRA should collect the Principal Investigator's formal acceptance to participate.

11.3 Site Initiation visit

Usually, a study initiation visit is planned to take place after all trial approvals (i.e. EC, Competent Authority and hospital approvals) have been obtained and all necessary study supplies (e.g. study documentation, drugs, and material, ISF etc.) are available at the site.

The SIV agenda to be provided to the site staff must cover all items present in the Site Initiation Visit Report and adequate time should be dedicated to protocol and main study procedures review (including study drug/material and biological sample handling/storage) and to the essential document's verification. The training on remote data capture and CRF completion is to be performed during the SIV.

11.4 First Monitoring Visit

The first monitoring visit must be planned just after the start of the treatment of the first patient at each participating site to prevent any mistake or misunderstanding regarding the trial conduct.

11.5 Monitoring Visit

Before each visit the CRA should ask the site staff to update as much as possible the e-CRFs, to send copies of drug accountability records, of the updated site Staff List, and of any essential document issued since the previous visit.

As part of the RMV preparation, the CRA will carefully review the clinical data entered in the CRFs to identify any major issues deserving further *on-site* verification, discussion with the site staff and/or re-training. Source data verification can be performed on randomly selected patients if no significant issues are detected, or on patients for which data issues have emerged.

- a) During the *on-site* monitoring visits the CRA will check the **Informed Consent Forms (ICF)** and **Patient Identification Log (T-CLI04-11)** of all patients enrolled since the previous visit.

Source data verification, i.e., the check of consistency between the data recorded in the e-CRFs and the original patient records at the clinical site, will be performed at each visit on the eligibility criteria and the primary study endpoint data of at least 5 patients (or of all patients treated since the last visit if less than 5). In addition, the CRA will review these patient records to detect any unreported Serious Adverse Events (SAE) or major protocol/GCP deviations.

Drug accountability and **Investigator File** will be checked only if discrepancies or missing items were found in the documents provided by the site staff before the visit.

- b) During the **remote** monitoring visits the CRA and the involved site staff will discuss any issues emerged concerning (but not limited to) the following:
- patient enrolment (e.g. reasons for accrual rate lower than expected, issues related to eligibility criteria compliance, etc.),
 - safety reporting (e.g., delays in SAE reporting),
 - e-CRF completion (e.g., systematic errors or clarifications needed about individual cases),
 - significant protocol deviations,
 - trial drugs management and accountability

During the phone call the CRA can ask the site staff to answer specific questions about individual patients' source data to ensure adequate data recording in the e-CRFs.

Additional details about specific items to be monitored are provided below.

11.6 Close-out Visit

The close-out visit is performed at each participating site when all issues and queries have been solved or justified by the PI.

Alternatively, the Close-out visits can be performed by phone and electronic documents exchange unless significant issues are still pending at trial end. In this case the CRA will ensure that all items listed in the COV Reports are duly fulfilled.

12 CASE REPORT FORMS (CRFs)

Case Record Forms (CRFs) will be completed by the Principal Investigator (PI) or authorized site personnel.

During the monitoring visit the monitor will check the CRF data against the source documents and will review the CRFs for completeness and accuracy.

A CRF is to be completed for ALL subjects who have signed the Informed Consent Form (ICF) and for whom clinical trial procedures have been started (i.e. physical exam, labs, etc.).

Screening failures will be defined as subjects who have signed the ICF but could not start the study treatment. A subject who is a screening failure, cannot be re-screened. For each screening failure the following CRF pages must be completed: <insert details on CRF pages to be complete>

12.1 Queries

Queries might be generated:

- by the CRA during the monitoring visit. These queries might be solved during the same monitoring visit.
- electronically by the system supporting the eCRF. They should be submitted by the PM or CRA to the site personnel for resolution that should occur as soon as possible, ideally before the following monitoring visit.
- after the data review done by the FROM – E.T.S. personnel (i.e. PM, biostatistician). Also in this case they are submitted by the PM or CRA to the site personnel for resolution that should occur as soon as possible, ideally before the following monitoring visit.

CRA's will be expected to handle and resolve queries on a regular and timely basis during the course of the study in order to avoid an unnecessary backlog developing shortly before database lock or center closedown.

Regular query resolution reports will be issued by FROM – E.T.S. PM/DM to assist in identifying outstanding queries. FROM – E.T.S. PM/DM will email queries in a .pdf file to the CRA who will bring them to the site for resolution. These queries should be faxed by the site to FROM – E.T.S. PM/DM upon resolution. The original signed query should be retained at the site in the patient files.

13 SOURCE DATA VERIFICATION (SDV)

Case report forms may NOT be used as source documents. Standard source documents for trials are Hospital/Medical records, Laboratory and other test results, Investigational drug receipt and return forms and individual patient's drug records etc. The CRA will work closely with site staff to define which documents will be considered source.

Data not collected in the patient/hospital file but reported directly in other documents should be documented on the Source Data Location List.

The CRA must ensure that all source data necessary for the verification of all protocol-required data are present at sites regardless of the format utilized to document the information.

For each patient the ICF (main study and sub-studies), eligibility criteria and serious adverse events will be 100% monitored against the patient source documents.

The first patient of each participating site will be monitored 100% for the first two visits.

If these CRFs are not acceptable (wrong data > 5% of verified data), 100% variables from following visits and for all ongoing patients at the site will be source verified until data quality is demonstrated.

The subsequent patients can be monitored partially as follows:

<specify one of the following three options:

Low risk - 10% (randomly) of the subsequent patients is monitored on the following data:

Medium risk - 30% (randomly) of the subsequent patients is monitored on the following data:

High risk - 50% (randomly) of the subsequent patients is monitored on the following data>

- Demography
- Medical history

- Concomitant medication
- Dose administration record
- Laboratory results

FROM E.T.S. will assess requirement of increased monitoring and oversight may be considered at the following sites:

- Extremely high randomizing sites
- Sites with significant study staff turnover (>25% annually)
- Sites with high numbers of SAE/AEs
- Sites with low or no AEs reported
- Sites with 3 or more unreported endpoints
- Sites with a significant number of Protocol Violations
- Sites with significant QA Audit findings

14 INFORMED CONSENT REVIEW

(To be completed at each visit for newly randomized patients)

For each patient the ICF (main study and sub-studies) will be 100% monitored against the patient source documents. The CRA will verify:

- the appropriate IRB has approved the Informed Consent Form in use.
- the most recently approved Informed Consent Form, as approved by the IRB, was signed and dated by the patient (or legal representative if applicable) and by the PI (or designee as applicable) prior to the initiation of any study-related procedures.
- consenting process is adequately documented in the patient source documents (e.g. clinical records)
- in case of ICF update the process for a re-consent of the patient has been performed and documented
- all signed Informed Consent Forms are filed in the patient's records at the study site and are available for an audit/inspection.

15 RANDOMIZATION PROCESS REVIEW

(To be completed at each visit for newly randomized patients)

For all patients enrolled, the CRA will perform the following verification of the randomization process:

- Verify subject eligibility
- Ensure that Inclusion/Exclusion Criteria are met for all randomized patients by reviewing the randomized patients' source data.
- Notify FROM – E.T.S. PM during the visit if any inappropriately randomized patients are identified. These patients must be documented accordingly as protocol violations in the monitoring report.

- Verify that the randomization number has been correctly assigned to each randomized patient. For any issues with incorrect randomization number assignment, contact the FROM – E.T.S. PM during the visit to report the issue. Ensure to investigate with PI how the error occurred and preventive action to be implemented by site to ensure it does not continue to occur.

16 PROTOCOL DEVIATION

Deviations from the protocol/GCP are not allowed. In case of doubt the Investigator must contact the FROM – E.T.S. PM or CRA. In case a deviation is detected this must be fully documented in the patient source document and in the CRF.

The CRA must inform the Principal Investigator and the PM of any critical deviation emerged during the monitoring activities.

Each deviation identified during the course of the trial is captured in the Protocol/GCP deviation log (T.CLI01.06). The log applies to all sites participating in the trial.

The PI is responsible for sending (i.e. email) the form to the FROM – E.T.S. PM as soon as a deviation occurs. The CRA should verify during the monitoring visit the notification of protocol deviations to FROM – E.T.S. In case the PI failed to inform FROM – E.T.S., the CRA should immediately inform the FROM – E.T.S. PM.

FROM – E.T.S. personnel evaluate the level of criticality and decides the corrective and preventive actions to be implemented in collaboration with the PI. They are reported by the PM on Protocol/GCP deviation log (T.CLI01.06) that is remitted to the PI for the implementation of the agreed actions.

In case of Phase I trials, critical deviations to conditions and principles of GCP and to trial protocol/amendments have to be notified by FROM E.T.S. Medical Director (within 7 days of the knowledge) to AIFA according to the Determina n.809/2015 dated June 19th, 2015.

Critical deviations are those likely to affect:

- the safety or physical integrity of the patients of the trial
- patient's rights
- the scientific value of the trial

In case of critical deviations, the corrective and preventive actions have to be implemented as a matter of urgency and documented.

17 DRUG ACCOUNTABILITY

The drug accountability checks should be in line with SDV and randomization schema (if any).

Trial specific forms will be provided for study sites to account for all study medication. They must be completed by either the center pharmacist or investigator/site personnel. Documentation of trial drug will be maintained for each patient.

The CRA should verify that these forms are properly filled in and duly archived. The CRA should also check the consistency of recorded information with the amount of unused IMP present at the Site. Any deviation must be notified and documented. The monitor should also check the IMP expiry date, the remaining quantity and give instructions as appropriate.

18 LABORATORIES

18.1 Local laboratory

The local laboratory of each participating site will be used to analyse urine and blood samples for routine clinical safety, while centralized laboratories might be used for biological samples (e.g. pharmacokinetic, pharmacogenetic, biomarkers, etc.).

For local laboratories the CRA will obtain local laboratory reference ranges and certificates. A copy will be filled in the ISF and in the TMF.

18.2 Central laboratories

< specify collection, storage and shipment of samples >.

- Ensure to check expiration dating on samples collection supplies.
- Ensure adequate supply of shipping forms, courier shipping supplies, etc.
- Ensure samples have been collected and handled according to protocol specifications and Lab Manual directives (if any).
- Ensure samples have been stored between <specify -xx°C and -yy°C> (PK samples to be stored between -20°C and -80°C)
- Ensure to monitor temperature recording log/device printouts to verify temperatures have been maintained in the range required by protocol
- In the event temperatures are missing from the log, discuss with site personnel reason for missing data and attempt to determine if data is available via an alternate source. Ensure to work with site personnel to implement action plan to ensure there are no missing data recordings in future.
- In the event of a temperature excursion, ensure to document as a deviation and contact the FROM – E.T.S. PM to report the deviation.
- Review all sample handling documentation to ensure samples are prepared in compliance with protocol and Lab Manual directives.
- Review all sample shipment documentation to ensure completed fully and accurately and including all required data.
- Review centrifugation equipment and verify current calibration to verify no issues.
- Ensure sample monitoring is completed prior to sample shipments dates. Ensure laboratory personnel understand the shipping requirements for samples.

19 INVESTIGATOR'S STUDY FILE (ISF)

The ISF must be reviewed for completeness and adequacy of the documents. The ISF content should be compliant with the structure provided in the FROM – E.T.S. ISF Index template (T-CLI06-02).

The Site Signature and Delegation Log (T-CLI04-06) and the Site Staff Training Record Site (T-GEN03-04) must be verified as frequent as possible.

20 PROCEDURE FOR AE AND SAE REPORTING

All Adverse Events will be documented for the period beginning with ICF signature and continuing through the trial period; AEs will be captured in the eCRF. Those events (clinical adverse event or abnormal laboratory test value) that are serious, occurring during the course of the study, irrespective of the treatment received by the patient, must be reported on the Adverse Event Report Form (in eCRF or, if not available, in the paper form) to the FROM – E.T.S. PM and <insert the name of the delegate> within 24 hours of the knowledge of the event occurrence.

General Instructions for SAE reporting

- the relevant information should be transcribed from the source documents onto the SAE form. It is not acceptable just writing “See attached” on the SAE form.
- FROM – E.T.S./delegate shall send request for clarification or follow-up to the CRA. The CRA shall contact the site and follow-up until query resolution is achieved. The CRA will liaison with site to ensure all follow-up requests or clarifications are addressed.

Clarifications to queries may be provided by the CRA via e-mail if not adding new safety data.

A follow-up response as well as follow-up data shall be provided by the PI through a follow-up SAE form within the same timelines as for initial SAE reporting.

- the CRA will fully source verify the SAE Report and instruct the site to update any discrepancies.

These instructions apply to initial and follow-up SAE reports.

In case paper SAE are used they must be delivered to:

FROM – E.T.S.:

PM name:

Phone:

Fax:

e-mail:

FROM – E.T.S. delegate for pharmacovigilance activities:

Reference person:

Phone:

Fax:

e-mail:

The CRA will ensure that the timelines of reporting are respected and that all SAEs have been reported and entered in the eCRFs.

21 MONITORING REPORT AND FOLLOW UP LETTER

21.1 Monitoring report

Monitoring visits should be documented by written reports. Reports must be written by the CRA within 5 working days of the visit, reviewed by the PM within 5 working days of the report receipt and approved by the FROM – E.T.S. Clinical Operations Coordinator. Monitoring activities and reporting procedure are according to the FROM – E.T.S. SOP CLI04 - Monitoring.

The original initiation visit report must be filed in the TMF and a copy must be filed in the Investigator Site File. The monitoring and close out reports are filed only in the TMF at FROM – E.T.S.

21.2 Follow up letter

After the approval of the monitoring report, the CRA should send a follow-up letter to the site or email listing the critical findings (protocol violations/deviations, deficiencies in the study conduct, inadequate patients care, underreporting of safety events, etc.), along with the corrective measures to be taken and recommendations/suggestions to ensure compliance.

22 TRIAL TEAM CONTACT TABLE

23 VENDORS
