CLINICAL DATA MONITORING PLAN (CDMoP)

PROTOCOL # [0000]

[TITLE]

CONTRACT RESEARCH ORGANIZATION

SPONSOR
[NAME]
[ADDRESS]

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1. PURPOSE

The purpose of this document is to specify all study specific monitoring requirements for [COMPANY] Protocol [0000] that ensure that the clinical sites comply with the study protocol and regulatory requirements.

2. REFERENCES

1. SOP XXXXX: Conducting Initiation, Monitoring and Closeout Visits
2. SOP XXXXX: Site Qualification
3. SOP XXXXX: Trial Master File
4. SOP XXXXX: Investigator Noncompliance
5. EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials (2010)
6. EMA Reflection paper on risk based quality management in clinical trials (2013)
7. FDA Draft Guidance for Industry - Computerized Systems Used in Clinical Investigations (2007)
8. FDA Guidance for Industry - Electronic Source Documentation in Clinical Investigations (2013)
9. FDA Guidance for Industry - Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring (2013)

3. STUDY ROLES AND RESPONSIBILITIES

Name	Contact Information	Role/Responsibility

4. TOOLS AND PROCESSES

4.1 Study Data

This study will use direct data entry of clinical trial data. This process allows a clinical study site to perform direct data entry of original data into EDC at the time of the subject's office visit, and for the original data to be stored in PDF format in the access-controlled data repository, access to which is controlled by the clinical Investigator or designee. These original data are stored in the access-controlled data repository prior to the data being transmitted to the EDC database.

4.2 EDC Monitoring Module

Monitors will record all monitoring reports in the online EDC system.

5. Risk Mitigation Strategy

Category	Risk	Severity	Probability	RPN	Risk Mitigation
Trial Outcome	Patient dosing compliance	high	medium	6	Instruction for user, site training prior to study, weighing of IMP, monitoring by CRO
Trial Outcome	Improper blood draw	high	medium	6	Training and monitoring of [DRUG] levels, online reports
Trial Outcome	Blood storage and processing at trial site	high	medium	6	On site monitoring
Trial Outcome	Missing blood draws on last day	high	medium	6	Monitoring, and training at interim visit immediately prior to 1st patient day 90, online reports
Trial Outcome	Patient dropouts	high	medium	6	Training and evaluating and resolving reasons for dropout, phone alerts prompted by eCRF, online reports
Both	Site staff misunderstanding of the protocol	high	medium	6	Training, reinitiate the site, assess the site after three patients treated, investigator meeting,
Trial Outcome	Unexpectedly low enrollment rate	medium	medium	4	Real-time monitoring of enrollment rate, allow for open enrolment across sites, online reports
Both	Incorrect dosing	medium	medium	4	Modify titration scheme and cut off based on previous data prior to study start for [0000], edit check in the eCRF, training, online reports
Both	Patient in other clinical trial	medium	medium	4	Use of verifiedclinical.com
Patient	Transfer to other individuals	high	low	3	Informed consent, instruction for user, site training prior to study
Trial Outcome	Errors in Bioanalysis at CRO	high	low	3	Auditing and review of data analysis turn around, communication plan
Trial Outcome	Loss of eSource data	high	low	3	Multiple daily backup and disaster recovery
Both	Improper enrollment of Ineligible patients	high	low	3	Central review and sign off patients by CRO when site confirms eligibility, not allow rescreening, review of medical record
Both	Improper reporting of AEs	high	low	3	Monitoring and review of patient records and medical record, online reports

Category	Risk	Severity	Probability	RPN	Risk Mitigation
Trial Outcome	Fraud and misconduct	medium	low	2	Monitoring
Trial Outcome	Error in application of IMP	medium	low	2	Instruction for user, site training prior to study, online reports
Both	Increase in safety lab test results	medium	low	2	Monitoring by investigator and daily by CRO
Both	Improper storage of IMP	low	medium	2	On site monitoring
Both	CRO staff qualifications	medium	low	2	Sponsor oversight
Patient	Overdose	low	low	1	Instruction for user, site training prior to study, drug accountability, online reports
Both	Skin reaction	low	low	1	Monitoring by investigator and daily by CRO, online reports
Both	Use of prohibited conmed	low	low	1	Monitoring review of medical record, online reports
Both	Site out of business	low	low	1	Contingency plan and proper qualification visit

6. SOURCE DOCUMENTS

1. Source data/records contain all the information necessary for the reconstruction and evaluation of the study. Source data/records are 1) original records, 2) certified copies of original records, 3) observations, 4) laboratory reports, 5) paper Case Report Forms (CRFs) and/or data sheets. In addition, with the use of direct data entry, the PDFs maintained in access-controlled data repository serve as original records. The EDC system and access-controlled data repository also support a process for certifying copies of records originally captured on paper.
2. At the time of the first monitoring visit or during the initiation visit, the source of original data, whether it is being collected in electronic or paper format, will be identified for each site.

7. MONITORING

Onsite monitoring visits will focus on assuring that the clinical site understands and is following the protocol, reviewing completeness and accuracy of Informed Consent Forms, drug supply reconciliation, risk-based source document verification (SDV) of original records, and other issues that may occur during the course of the clinical trial.

Central monitoring will focus on the assessment of 1) the “reasonableness” of data entered into EDC system and 2) data quality management metrics

7.1 Onsite Monitoring

All onsite monitoring visits will be planned, but they will not follow a fixed schedule. For each site, the Project Manager or the responsible monitor, will schedule the first onsite monitoring visit to coincide with the first PK blood draw (Day 1) for any of the first three subjects. Based on the findings at this visit, coupled with central monitoring findings, the Project Manager will decide when to schedule the next monitoring visit.

For each site, the Project Manager will schedule a monitoring visit immediately prior to or coinciding with the first subject’s 24-hour PK blood draw (Day 90/91). The purpose of this visit is primarily to retrain the site personnel on the relevant study procedures.

Interim monitoring visits will include review of the following:

1. Informed Consent process and Forms (100%)
2. Study conduct and protocol adherence
3. Subject Eligibility (100%)
4. Adverse events (100%)
5. Drug supply accountability (100%)
6. Temperature logs
7. Personnel delegation and signature log
8. Patient medical records

9. Protocol deviations and violations
10. Follow-up of outstanding issues
11. The certification process of data originally collected on paper and subsequently entered into the EDC system

Where the site maintains patient records that duplicate information captured in the EDC system, the monitor will review those records specified below to ensure that the site records match those captured in the EDC system:

1. Demographics (100%). To ensure subject identities based on the site's medical records
2. Medical History. To ensure the sites have entered into the EDC system all relevant inclusion/exclusion criteria (100%)
3. Confirmation of subject's visit to the clinical site (100% of first 3 subjects)
4. Review of office medical record (100% of first 3 subjects)

When findings indicate that retraining is required, the monitor must retrain site staff as soon as possible, and if necessary the site will be informed not to enroll additional subjects until successful completion of the training.

7.2 Central Monitoring

Monitors will perform daily in the EDC system:

1. 100% review of all entered forms and issue queries if needed
2. Review and take appropriate action for all online and batch edit checks
3. Review of baseline and titration [DRUG] against records received from central laboratory Levels (100%)

Monitors will issue weekly central monitoring reports to record issues identified through daily monitoring activities.

Monitors will review periodically the eTMF for accuracy and completeness.

Quality by Design (QbD) meetings will take place on a weekly basis with the Project Manager, Project Director, Biostatistics (as needed), and Data Management (as needed) to review the progress of the clinical trial. Items to be reviewed at the QbD meetings may include:

1. Enrollment and dropout status
2. Number of forms entered and reviewed
3. An assessment of edit checks and queries that are being fired, by form as well as by variable
4. Reasons for changes to the database by the clinical site
5. Adverse events
6. Medications
7. Protocol deviations and violations

8. Monitoring Procedures
9. Other items that may arise
10. Action items

The Project Manager will record meeting minutes and follow-up actions. The schedule of meetings and the Clinical Monitoring Plan may be modified depending on findings. The decisions and the rationale for changing any of the procedures will be documented.

7.3 Qualification Visit

The purpose of the qualification visits is to assess the clinical trial sites ability to fulfill the qualification criteria. Decisions regarding the need for onsite qualification visits will be made in accordance with SOP XXXXX.

7.4 Site Initiation Visit

The purpose of the study initiation is to train Investigators and site personnel on the specific requirements and procedures needed to perform the clinical trial.

Site initiation will occur at the Protocol Investigator Meeting (PIM), locally at specific sites who do not attend the PIM, or if it is determined that a specific site requires additional training. Sites will not enroll subjects into the trial until the site initiation has been satisfactorily completed. Delivery of the investigational product may precede the initiation, but must not be shipped until the study site receives IRB approval.

At a minimum, the agenda for the site initiation visit must include the following elements:

1. Review of the protocol
2. Training appropriate staff on:
    a. GCP regulations
    b. SAE reporting requirements
    c. Investigator on the Investigator responsibilities listed on the FDA Form 1572
    d. Investigational product handling procedures
    e. Weighing of the Investigational Product
    f. Subject management over the course of a 24-hour PK
    g. Handling of PK samples
    h. Handling of safety laboratory samples
    i. EDC system
    j. Certification of original records
    k. Maintenance of the electronic Trial Master File (eTMF)
    l. Direct data entry process

7.5 Interim Monitoring Visits

The purpose of interim monitoring visits is to ensure that the 1) rights and well-being of each subject are protected, 2) trial data are accurate, complete and verifiable, 3) the trial is

conducted according to ICH GCP guidelines, and 4) that the trial site and staff remain trained and qualified. Monitoring of the clinical trial can occur both by onsite visits as well as through central monitoring procedures.

7.6 Closeout Visit

The purpose of the closeout visit is to bring to official completion all trial-related activities at the site.