Management of Deviations
From Onsite Monitoring to Clinical Study Report Proposal for an integrated process

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Background

• Definition

ICHE6: Compliance is defined as adherence to all the trial-related requirements, GCP requirements, and the applicable regulatory requirements.

A deviation is a lack of compliance with any of the above.
Background

• Lack of traceability of deviations
  • To be followed during on-site monitoring visits
  • To be centrally monitored (using data collected through CRF) during a data review meeting
  • To be used for analysis
  • To be reported in the clinical study report

Background

• Lack of “sponsor” definition
  – leading to inconsistencies between studies as regard classification rules (minor vs major)
• Lack of overall process
Background

• Need to “use” a standard terminology whatever the steps and actors included in the trial:
  – At site and corporate level,
  – During the conduct of the trial,
  – In the clinical study report

Sponsor definition

<table>
<thead>
<tr>
<th>Important</th>
<th>Conditions, practices or processes that might harm/violate the rights, safety or well being of subjects/patients and/or the quality and integrity of data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>Conditions, practices or processes that would not be expected to harm/violate the rights, safety or well being of subjects/patients and/or the quality and integrity of data. Observations in this category are typically isolated events and do not involve frequent or systematic deficiencies.</td>
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## Some Examples

### Important
- There is no evidence in the source documents that a physical examination was performed in a subject at a time required by the protocol.
- Clinical trial centers were initiated prior to the availability of the monitoring plan.
- The treatment taken by the patient does not correspond to the one allocated by the IVRS.
- Deviations in a selection criterion defining the targeted population.
- Patient taking prohibited concomitant medication.

### Other
- Some isolated inconsistencies exist between the source documents and the case report form, which do not impact the primary study criterion or the safety evaluation.
- A study document is not identified by a date and a version number.
- Patient visit performed outside time windows.
Background

• Need for a formal integrated process
  – Guideline describing the management of deviations in clinical trials from onsite monitoring to clinical study report

Central Data Review

• Ongoing central monitoring of clinical data
  • Focus on data quality issues
  • Surveillance aspect (identification of issues and implementation of corrective actions)
  • Monitoring and follow-up of deviations is a key component
Central Data Review

- Feedback to monitoring teams formalized
- Action plan communicated
- All deviations are loaded in the Clinical Database (CDISC compliant)

Focus on Central Data Review & Exchange with Monitoring staff

- Qualitative Deviations (monitoring visits)
- Quantitative deviations (derived through CRF data)
Reporting in the clinical study report

• ICH definitions
  - E3 : All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or assessments should be described.

  - E9 : Handling of protocol deviations in the statistical analysis of clinical data

• Quantitative deviations:
  - Directly identified using clinical data recorded in the CRF and based on central data review before unblinding and the final version of the statistical analysis plan (SAP)

  - Include important deviations impacting efficacy analysis and randomization/dosing irregularities, as per SAP, as well as deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or assessments
Reporting in the clinical study report

• Qualitative deviations:
  - Directly reported by the monitoring team or discovered during audit, and assessed by the clinical trial team during the central data review process
  - Only deviations considered as important during the central data review are summarized in the clinical study report (eg, informed consent issues, site closure due to non-compliance, fraud etc)

Conclusion

• This integrated process will allow:
  - Consistent monitoring of deviations (on site or centrally) in order to take appropriate actions
  - Improved traceability of deviations from investigator site to clinical study report