Conducting and reporting a GCP Inspection

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Preparation for an inspection

- Inspection plan

- Create worksheets for the inspection
  - general
  - project specific
  - study specific

Preparation for an inspection

- Choose study/site
  - studies according to inspection plan
  - number of included patients
  - problems
  - other studies
  - location
  - when in the lifecycle of the study

Inspection – which trial

- Primary safety and efficacy trials for market authorisation
- Randomly selected trials
- For cause

Criteria for site selection

- High enrolment of subjects
- Multiple trials conducted by investigator
- Country representation
- Non-compliant investigator
- Unusual trends in analysis/efficacy data, enrolment, drop-out rate, SAE

Preparation for an inspection

- Announce the inspection
  - who should be informed
  - when
  - how

Preparation for an inspection

- Documents to read before the inspection
  - protocol and amendments
  - CRF and diaries
  - CRF guidelines
  - monitoring manual
  - Investigator’s Brochure

Preparation for an inspection

- Documents to read before the inspection
  - study specific documents/manuals
  - contracts/agreements
  - shipping documents
  - monitoring reports
  - SAE

Preparation for an inspection

- Travel arrangements
- Who is going to participate
  - internal
  - external
- Start writing the report

Inspection - how

- Conduct of inspection
  - Facilities
  - Investigator File
  - Source Data Verification

Investigator Site Inspection Process

- Opening meeting with investigator and research team
  - introduction
  - objective of the inspection
  - logistics
  - attendance
  - Investigator to outline responsibilities, training of staff
  - Investigator to explain study conduct, procedures and documentation

Investigator Site Inspection Process

- Inspection Questioning techniques
  - Conversational
  - Interview
  - Interrogation
  - Open questions
  - Closed questions
  - Clarifying
  - Forced

Investigator Site Inspection Process

- Review of Investigator File
  - resources and qualification of site personnel (CV)
  - responsibilities at the site (signature/delegation lists)
  - monitoring
  - laboratory
  - pharmacy (dispensing records, storage)

Investigator Site Inspection Process

- Rights, safety and well-being of the subjects:
  - IEC approval
  - Informed consent procedure and documentation
- Investigator's brochure
- Adverse event reporting

Investigator Site Inspection Process

- Source Data Verification (SDV)
  - Consistency between source documents and CRF
  - Protocol adherence

Inspection - how

- Closing meeting
  - feedback
  - issues
  - observations
  - recommendations for corrective actions

How is an inspection conducted? - after

- report submitted to investigator and sponsor
  - normally within 30 days
- response requested from investigator and sponsor
  - normally within 30 days
- the case is closed

Sponsor site inspection

Inspection – which processes/systems

- At sponsor site
  - clinical trial process
  - adverse event
  - investigational products
  - data management and statistics
  - computer systems
- At contacted facilities
  - dependent on services provided

Inspection at Sponsor Site

- File
- Protocol ↔ CRF
- Amendments
- Approvals
- Agreements
- Investigational product
- Monitoring
- Adverse event reporting
- Data listings
- Clinical study report

How do we plan a sponsor site inspection?

- Prepare a trial specific adjusted Inspection Plan
  - Organisation and personnel
  - Standard Operating Procedures
  - Specific Aspects of the Clinical Trial inspected
    - Development and set-up of the clinical trial
    - Clinical trial management and monitoring
    - Data handling
    - Safety and adverse events reporting
    - Independent Drug Safety Monitoring Board
    - Trial documents
    - Investigational Medicinal Product
    - Auditing

How do we conduct a sponsor site inspection?

- Organisation and personnel
  - Focus on the specific clinical trial
  - Request organisation charts with staff names and brief summaries of responsibilities directly related to trial activities
  - Select few persons for review of CVs and training records
  - Request an overview (with location) of all company facilities involved in clinical trial activities (for this clinical trial), including key service providers, CROs and support services

How do we conduct a sponsor site inspection?

- Standard Operating Procedures
  - Request a SOP index and the SOP on production of SOPs
  - Select and request the most important ones for a systematic review, e.g.:
    - Clinical trial management
    - Quality Control and Quality Assurance
    - Data Management
    - Management/supply of IMP
  - Consider a review of additional guidance documents (SOPs, SIPs, working procedures, etc.) prior to the inspection

How do we conduct a sponsor site inspection?

- Specific Aspects of the Clinical Trial inspected
  - Development and set-up of the clinical trial
    - Review the preparation, review and approval processes for protocol, CRF, IB and other relevant documents
    - Important issues re amendments and changes during the trial, e.g.:
      - Not each individual inclusion criteria adequately reproduced in the CRF => reason?
      - Definition for protocol violations not provided in the protocol => where else?
      - Ambiguous definition of IMP dose adjustments => Amendment?

How do we conduct a sponsor site inspection?

- Clinical trial management
  - Delegation and outsourcing of trial related duties
    - select vendors for review of contracts at sponsor site
  - Investigator selection
    - responsibility, feasibility check, selection criteria, documentation
  - Training of investigational site personnel
    - when, where, how, who
    - compare training material used for different regions

How do we conduct a sponsor site inspection?

- Conduct of the clinical trial and monitoring
  - Request and review the Monitoring Plan
  - Review if any relevant issues observed during the investigator site inspections
    - Reporting and follow-up of problems observed by monitor
    - Corrective actions taken by sponsor
    - Documentation and reporting of protocol violations

How do we conduct a sponsor site inspection?

- Data Handling
  - Request and review the Data Management Plan
  - Request and review the Statistical Analysis Plan(s)
  - Request a listing of ALL protocol deviations (if not provided with the CSR)
  - Compare with information reported in the Clinical Study Report (in particular sections “9.8 Changes in the Conduct of the Study or Planned Analyses” and “10.2 Protocol Deviations”)
  - Review of clinical trial database, check available edit checks on e.g. inclusion/exclusion criteria
  - Review the “query” system

How do we conduct a sponsor site inspection?

- Independent Drug Safety Monitoring Board
  - Request and review the DSMB working procedures
    - Members of the DSMB
    - Communication with sponsor
  - Request and review the DSMB meeting minutes
    - Which data was provided to the DSMB? When?
- Auditing
  - Review the CSR for information regarding audits
  - Review at the sponsor site:
    - audit plans: planned vs. performed
    - conduct of pre-selection audits of vendors
    - audit report for any non-compliant investigator site, if any

What are the outcomes of a sponsor site inspection?

Recent examples:

- Lack of a clear definition of a “protocol violation / deviation / exception / waiver”
- Protocol waivers for enrolment of non-eligible patients granted prospectively by the sponsor
- Protocol violators included in the “evaluable population” or Per Protocol population for the efficacy analysis
- Edit checks not programmed adequately, plausibility cross-checks had to be performed manually => potential source of error
- Assessment of the relatedness of SAEs performed by sponsor personnel, who did not have access to all available information concerning the IMP

Summary and recommendations

- Always plan a sponsor inspection to be the last one
  => use the experience from investigator site inspections
- Use an adjusted Inspection Plan
- Plan sufficient time for inspection preparation
- Prepare as much as possible prior to the inspection
  - Complex structure of the sponsor organisation
  - Review of documents prior to the inspection enables to use the time at the sponsor site for interviews with relevant personnel

Inspection of sponsor sites in multicentre trials

is the only possibility to gain an overview of the quality management system of the sponsor and its effectiveness

Inspection report

Inspection Report

- Observations related to non-compliance to GCP and regulatory requirements
- Comments to improve quality
- Recommendations for corrective actions and suggestions for improvement

Inspection report requirements

- Must be the up most quality
- Must bring added value
- Must be clear and understandable
- Must reflect the conduction of the inspection

Inspection report requirements

- Must evaluate the compliance with local regulations, GCP, ethical and scientific standards

- Must evaluate the validity and reliability of the data recorded/submitted according to the scope of the inspection, answering all the questions asked in the inspection request

Conclusion of the Inspection Report

Conduction, recording and reporting of the trial acceptable/non-acceptable according to the principles of GCP

If the inspection is related to MA, a recommendation should be given on whether the quality of the reported data allows its use in a MAA

Content of an Inspection Report

- A. Administrative Information.
- B. Background and general information
- C. Administrative aspects of the trial.
- D. Trial documents
- E. Conduct of trial.
- F. Documentation and reporting of data
- G. Accountability of medicinal products
- H. Laboratories, technical departments.
- I. Monitoring and auditing
- J. Summary, discussion and conclusions.
- K Dates and signature(s) of Lead inspector and other inspector(s)
- L. Appendices:

  Response from the sponsor/investigator

  Other appendices as required

Classification of findings

- Critical deviation
- Major deviation
- Minor deviation
- Observation

Critical deviation (EMEA)

Conditions, practices or processes that **adversely affect** the rights, safety or well being of the subjects and/or the quality and integrity of data.

Critical observations are considered totally unacceptable.

Possible consequences: rejection of data and/or legal action required.

Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Fraud belongs to this group.

Major deviation (EMEA)

Conditions, practices or processes that might adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Major observations are serious deficiencies and are direct violations of GCP.

Possible consequences: rejection of data and/or legal action required.

Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

Minor deviation (EMEA)

Conditions, practices or processes that would not be expected to adversely affect the right, safety or well being of the subjects and/or the quality and integrity of data.

Possible consequences: Observations classified as minor, indicate the need for improvement of conditions, practices and processes.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

Observation (EMEA)

The observations might lead to suggestions on how to improve quality or reduce the potential for deviation to occur in the future.

Managing site inspections

- Notification of the inspection to all personnel
- Participants should be available within reasonable time
- Confidential area for inspection
- Ask what specifically the inspectors wishes to view
- (Present only items asked for)
- (Visit only areas that are relevant)

Managing site inspections

- Best way of preparing for audits and inspections is by:
  - protecting your subjects and generate credible data by:
    - Follow country laws and regulations
    - Comply with GCP
    - Adhere to the protocol

Fraud, Misconduct, Sloppiness and Human mistakes at Investigational Sites

Fraud

1. crime of cheating somebody: the crime of obtaining money or some other benefit by deliberate deception

2. somebody who deceives: somebody who deliberately deceives somebody else, usually for financial gain

3. something intended to deceive: something that is intended to deceive people

Misconduct

1. immoral, unethical, or unprofessional behaviour: behaviour that is not in accordance with accepted moral or professional standards

2. incompetence: incompetent or dishonest management of something, especially on behalf of others

Sloppiness

1. Messy or careless: behaviour indicating lack of care or effort

Glossary

- Fabrication: Invention of data or cases
- Falsification: wilful distortion of data
- Plagiarism: copying of ideas, data or words without attribution

Why would anyone commit fraud or misconduct?

- Personal gain
  - financial
  - scientific
  - vanity/egoism
- Cover-up of mistakes
  - carelessness
  - incompetence
- Stupidity
- Monitor's pressure

Fraud and misconduct

- Patient does not exist
  - patient records fabricated
- Test not performed
  - recording of test fabricated
- Test from other patient or other time
  - same test from another patient used
  - results from a test at an earlier visit repeated
- Incorrect dating
  - dates and events do not match

How to spot fraud and misconduct

- Generally it is a gut feeling
  - Observe – be open and aware
  - Use your probing skills
  - Analyze, verify, investigate and evaluate
  - Report and act

How to spot fraud and misconduct

- Too perfect
  - everything is perfect
- Records do not match
  - conflicting data
- Records never available
  - patient always visiting another department
- Investigator behaviour
  - nervousness

Primary prevention

- Education and Training
  - GCP (ICH, WHO or other), SOPs and Ethics
- Create an “open” environment
  - Establish and maintain good working relationship with the site staff
- Introduce checks and balances
  - Efficient monitoring, auditing , IDMC

Fraud and misconduct

- Fraud and serious misconduct exist, but is very rare.
- Few people take on a task with the intention of doing a bad performance.
- Sloppy performance is not fraud or misconduct.
- Mistakes are just normal human behaviour