AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

GCP Inspections

Angela Del Vecchio

24/05/2019

Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	X	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	X	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	X	☐	☐	☐ facoltativo
2. Consulenza per una società	X	☐	☐	☐ facoltativo
3. Consulente strategico per una società	X	☐	☐	☐ facoltativo
4. Interessi finanziari	X	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	X	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	X	☐	☐	☐ facoltativo
7. Sperimentatore	X	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	X	☐	☐	☐ facoltativo
9. Interessi Familiari	X	☐	☐	☐ facoltativo

* Angela Del Vecchio, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 25.03.2015 e pubblicato sulla Gazzetta Ufficiale del 15.05.2015 in accordo con la policy EMA /626261/2014 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. <Per questo intervento non ricevo alcun compenso>

Overview

- References
- Investigator's site inspection (preparation, conduction)
- Clinical Trial Pharmacy Inspections
- Sponsor site inspection (preparation, conduction)
- Inspection Report
- Common findings

References

- Note for guidance on Clinical Practice CPMP/ICH/135/95 GCP -R2
- (D.Lvo 211/2003) Directive 2001/20/EC
- (D.Lvo 200/2007) Directive 2005/28/EC
- Annex 13 GMP February 2010
- Eudralex, vol.10 - CTs, of Rules Governing Medicinal Product in the EU, in particular

Guidance documents containing the commom provisions on the conduct of GCP inspections by CA of different member states

AIMS

To guarantee the rights, safety and well-being of study subjects

To ensure that clinical data are credible and reliable

Different types of GCP-inspections

- ✓Investigator site
  - Pharmacy
  - Ethics Committee
  - Laboratory
  - Phase I Unit
- ✓Sponsor/CRO site

When?

- ✓ Inspection before the approval of a clinical trial
- ✓ Inspection of an on-going/finished clinical trial
- ✓ Inspection within the context of a marketing authorisation process

  -National Procedure
  -Mutual Recognition Procedure
  -Decentralized Procedure
  -Centralized Procedure

INVESTIGATOR'S SITE INSPECTION

ISI

PREPARATION FOR AN ISI

Inspection announcement

- Letter to the investigator/sponsor/applicant
- Legal framework and reason of the inspection
- Confirmation of inspection site/dates

- Documents request

-protocol and amendments
-CRF, diaries, questionnaire
-sample patient information sheet and consent form
-Investigator's Brochure
-monitoring plan/SOPs and monitoring reports
-contracts/agreements
-shipping documents
-SAE
-complete final Clinical Study Report with tables and appendices
-individual patient data listings for all patients recruited at the specific clinical trial site

PREPARATION FOR AN ISI

The Inspection plan

- The inspection plan generally outlines and defines the relevant aspects of the clinical trial site and scope that are to be covered during the inspection. It is based on the inspection scope and the reviewed documentation. It is an internal working document for the inspection team to guide through the inspection.

- Summary of all questions to be addressed and documents to be reviewed during the inspection

PREPARATION FOR AN ISI

The Inspection plan

- The Inspection Plan includes:
- ✓ information received from assessors

- ✓ information taken from:
  - the application
  - the document requested before the inspection
  - the EUDRACT database

- ✓ results from the comparison of different documents:
  - CSR vs.data listing
  - Visit dates vs. drug administration dates
  - Protocol deviations vs.patient excluded from analysis
  - Study documents/monitoring reports/

PREPARATION FOR AN ISI

Arranging the inspection

- Agenda: interviews, document review and tour through the facilities

  -availability of principal investigator and key personel from site/monitor/sponsor

- Availability of source data/medical files/CRF/investigator's file

- Travel arrangements

CONDUCT OF AN ISI

3-5 days

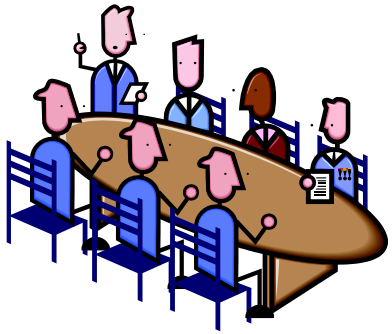
Typical Agenda

- Opening meeting
- Interview with the PI and site staff
- Review of Investigator's File
- Source data verification
- Visit to Pharmacy facilities
- Visit to Clinical Facilities
- Visit to Laboratory (if applicable)
- Inspectors meeting
- Closing meeting

CONDUCT OF AN ISI

Opening meeting with the principal investigator and site staff

- Introduction, regulatory framework for the conduct of the inspection
- objective of the inspection
- Logistics
- Questions
- Investigator's introduction



CONDUCT OF AN ISI

Interviews with PI and site staff

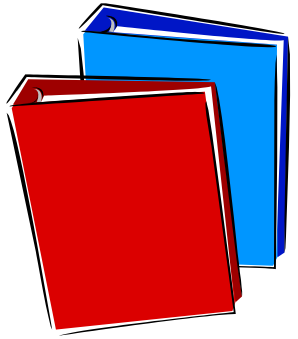
- roles and responsibilities
- training
- GCP/legislation knowledge
- trail procedure (inclusion of subject, consent procedures, IMP management)
- safety reporting
- archiving

CONDUCT OF AN ISI

Review of the Investigator's File

Essential documents §8 GCP

It serves to demonstrate the compliance of the investigators, sponsor and monitor with the standard of GCP and with all applicable regulatory requirements



- ✓ Authorisations, EC approval, informed consents
- ✓ Protocol and amendments
- ✓ Qualification of site personnel (CV)
- ✓ Investigator's Brochure
- ✓ Insurance statement
- ✓ Delegation list
- ✓ Shipping, accountability, dispensing records, storage
- ✓ Normal Values/Ranges for medical/laboratories porcedures
- ✓ Subject screening and enrolment log
- ✓ Adverse event reporting

CONDUCT OF AN ISI

Source data verification (SDV)

- Consistency between source documents and CRF
- Protocol

1.11 Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.52 Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, ...subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

CONDUCT OF AN ISI

Review of Facilities

- Tour of clinic
- Equipment used
- Sample processing/storage
- Pharmacy/IMP storage
- Other units

CLINICAL TRIAL PHARMACY INSPECTIONS

(CTPI)

CTPI

General aspects

- The inspection at the Hospital Pharmacy is conducted during the inspection at the Investigator site in the second or third day

- The inspection is focused on the CT that is inspected in the investigator's site and on general management of IMPs

- At least 1 pharmacist must take part in the inspection

- The pharmacist must be on duty at the Hospital Pharmacy and must be aware of the Investigational Medicinal Product(s) management

CTPI

General aspects

The inspection is composed in three parts:

1. Meeting with the pharmacist(s) involved in the IMP management
2. Review of the documentation related to the trial object of the inspection
3. Visit of the Pharmacy

CTPI

1. Meeting

The purpose of this meeting is to:

- Introduce the inspector(s) to the inspectee(s).
- Confirm that the resources, documents and facilities needed by the inspector(s) are available.
- Have information about the IMP management into the hospital pharmacy (receipt, storage, distribution and destruction)

CTPI

Furthermore....

... the inspectors have to:

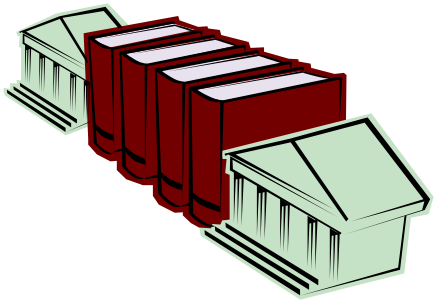
- Confirm whether the management of the IMP is in compliance with GCP, verifying registrations, electronic or on paper;
- Confirm whether there are SOPs in place;
- Confirm that there is a sufficient number of pharmacists compared to the number of clinical trials conducted in the hospital.

CTPI

2.Review of the documentation

The inspectors verify all the documents related to the IMP used in the clinical trial.
To be considered:

- Drugs shipment notes from the Sponsor with the relative receipts. The notes should contain batch numbers, expiry date and patients code numbers (if applicable)
- Drugs shipment notes from the pharmacy to the Investigator and, if necessary, drugs shipment notes from Investigator to the pharmacy about unused drugs
- EC approval
- CT Protocol



CTPI

2.Review of the documentation

❖Accountability form

➡ IMP amount delivered to the pharmacy, amount dispensed at the investigator's site and, if it is the case, IMP amount returned to the pharmacy (including batch numbers, expiry date and code numbers)

➡ Documentation related to re-labelling (if applicable)

➡ IMP amount returned to the Sponsor, if applicable, (including batch numbers, expiry date and code numbers)

❖ Documents of drug destruction (if applicable)

CTPI

3. Visit to the Pharmacy

After the end of the review of the documentation, the inspectors should visit the pharmacy places in which the IMP is managed

To be considered:

- Whether the IMP is maintained in a cabinet accessible only to the hospital pharmacy personnel and if it is identified as IMP and is separated from other drugs;
- Whether necessary, the IMP is maintained, separated from other drugs, in appropriate fridge or freezer;
- Whether the fridge/freezer temperature is monitored and recorded

CONDUCT OF AN ISI

Closing meeting

At the end of the inspection, the inspector(s) should hold a closing meeting with the inspectee(s).

The main purpose of this meeting is to present inspection findings to the inspectee(s) and to ensure that the results of the inspection are clearly understood and that there are no misunderstanding by either the inspector(s) or the inspectee(s).

-Feedback
-Issues
-Observations
-Recommendations for corrective actions

SPONSOR SITE INSPECTION

SI

PREPARATION FOR SI

Two different approaches

- System inspection
- Specific Clinical trial inspection

PREPARATION FOR SI

System inspection

To evaluate the quality system established by the sponsor in order to assure that CTs are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirements.

Of course it is necessary to use as an example of the system, documents/data from specific trial.

PREPARATION FOR SI

Specific Clinical trial inspection

To verify if the trial has been conducted, data has been generated, documented and reported in compliance with the protocol, GCP and sponsor procedures.

In any case even if the inspection is specific for the study, the inspectors have to verify the Sponsor QUALITY SYSTEM applicable at the time of the specific trial.

PREPARATION FOR A SI

Inspection announcement

- Letter to the sponsor/applicant
- Legal framework and reason of the inspection
- Confirmation of inspection site/dates
- Documents request

-complete final Clinical Study Report with tables and appendices
-individual patient data listings for all patients recruited
-relevant key SOPs (in place at the time of the study)
-monitoring plan/SOPs and monitoring visit reports
-contracts/agreements
-SAE

PREPARATION FOR SI

The plan

- Prepare the agenda, with approximate timings and names of those nominated for interview
- Plan ahead to ensure that the relevant people are present in interviews
- Organization to understand that the plan is flexible
- The plan can be reviewed at the end of every day

Example of Agenda

Agenzia Italiana del Farmaco
AIFA

GCP Inspection on XXX Sponsor's site (date)

Site to be inspected XXX

GCP Inspectors XXX

1st Day – (date)	**Timing***	**Personnel to be interviewed**
Opening meeting, and short introduction of the inspection with sponsor's representative	9.00 -9.30	
Short overview of general Organisation of the Company in particular referring to Clinical Research activities and to the study XXX– Overview of the study XXX	9.30– 10.00	
Outsourcing, Contract management, selection and procedures for contracting trial-related duties, focusing on study XXX	10.00 -11.00	
SOP management	11.00 -12.00	
Overview of IT systems applied in clinical trials	12.00 -12.30	
Lunch	12.30 -13.30	
Personnel Training	13.30 -14.00	
Project management	14.00 -17.00	
Document review	17.00	

Inspection Process at Sponsor site

3 to 5 days

- Opening Meeting
- Interview Sessions
- Document Review
- Facility Visits
- Closing Meeting

Areas to cover

•General organization of clinical research	•Data management
•SOPs Management	•Medical Writing
•Training	•Statistical Analysis
•Clinical Trial Management	•Pharmacovigilance
•Contract Management	•IMP Management
•Monitoring	•Quality Assurance
•Computer System	•Archiving

CONDUCT OF A SI

Opening meeting

- introductions
- confirm purpose of inspection
- explain the regulatory framework for the conduct of the inspection
- review inspection plan & methodology
- confirm that the resources, documents and facilities are available
- confirm the time and date for the closing meeting
- questions

CONDUCT OF A SI

During the inspection

- Interview sessions

Sponsor personnel involved in different topics

- Documents review

SOPs, CVs, Job descriptions, contracts, CSRs, monitoring plans, SAEs CR, etc.

- Facility visits

workplaces involved in clinical trials, e.g. archives, IT, IMP, PHV, Data Management

CONDUCT OF A SI

During the inspection- Documents

AIFA	AGENZIA ITALIANA DEL FARMACO Ufficio GCP

DOCUMENTI RICHIESTI IN CORSO D'ISPEZIONE

Azienda ispezionata:	
Data dell'intervista:	

Foglio

N.	Richiesto da	Descrizione documento	Ricev.	Visto	note

CONDUCT OF A SI

During inspection

- Inspection plan as a guide
- Flexible in the way of approaching the situation
- Open minded dialogue from the start
- A continue feedback throughout the inspection
- Brief of the outgoing inspection

CONDUCT OF A SI

✘ Organisation and personnel

- ✓ Overview (with location) of all company facilities involved in clinical trial activities (for this clinical trial), including contracts with CROs
- ✓ Organisation charts with staff names and brief summaries of responsibilities directly related to trial activities
- ✓ CVs and training records for some sponsor personnel
- ✓ Training plan
- ✓ SOP Training

CONDUCT OF A SI

- Standard Operating Procedures

  - ✓SOPs list and the SOP on production of SOPs
  - ✓SOPs draft, review, distribution, storage
  - ✓Global and local SOPs
  - ✓Additional documents (working procedures)

CONDUCT OF A SI

- Clinical Trial Management
  - ✓ Delegation and outsourcing of trial related duties
    - *Review of contracts*
  - ✓ Investigator selection and agreement
    - *Responsibility, selection criteria*
  - ✓ Training of investigational site personnel
    - *Training material used*

CONDUCT OF A SI

✓Preparation, review and approval processes for protocol, CRF, IB, amendments and other relevant documents

✓Regulatory submissions

- *EC Approval*
- *CA authorisation (where required)*
- *Submission and approval of amendments*

CONDUCT OF A SI

- Monitoring
  - ✓Monitoring Plan /SOPs
  - ✓Monitoring activities
  - ✓Monitors'qualification
  - ✓Monitoring reports and review of the reports by the sponsor
  - ✓Corrective actions taken by sponsor

CONDUCT OF A SI

- Data Handling and Medical writing
  - ✓Data Management Plan
  - ✓Validation of computer system used
  - ✓Statistical Analysis Plan
  - ✓List of all protocol deviations (if not in the CSR)
  - ✓Quality control of CSR

  - ✓Visit to Data Management/Statistics department(s):

    CT database
    CRFs receipt/tracking/entry
    Query system
    Storage areas (CRFs, Randomisation Codes etc.)

CONDUCT OF A SI

- QA and Auditing
  - ✓Audit of key CT processes
  - ✓Pre-selection audits of contractors
  - ✓Auditors'qualification
  - ✓Audit plans: planned vs performed
  - ✓Audit reports and processes for communicating audit findings
  - ✓Audits information in the CSR

CONDUCT OF A SI

- Pharmacovigilance
  - ✓Notification, follow up and reporting of SAEs/SUSARs
  - ✓Reconciliation process between CT database and PVH database
  - ✓Updating of the safety information in the Investigator Brochure

CONDUCT OF A SI

- IMP management
  - ✓Manufacturing, packaging, labelling
  - ✓ Supplying, accountability, returns and destruction
  - ✓Storage and transport
  - ✓Randomisation and code breaking
  - ✓Blinding

CONDUCT OF A SI

Archiving

- ✓System for archiving and retrieval of documents
- ✓Controlled access to archives
- ✓All essential documents available are in compliance with Eudralex, vol. 10, chapter V

CONDUCT OF A SI

Closing meeting

- ✓Present the inspection findings to the inspectees and clarify any misinterpretation
- ✓Opportunity for the Company to clarify the findings
- ✓Explain the circulation of the inspection report (deadline)
- ✓Questions

INSPECTION REPORT

Inspection report

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

Inspection report requirements

- Must be clear and understandable
- Must reflect the conduction of the inspection
- Must evaluate the compliance with (EU and) national 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, e.g. CHMP, National Authority (MA Unit, etc.)

Inspection report

- Investigator site (Pharmacy, laboratory, EC)
- Laboratory
- Sponsor /CRO site

Different formats
(national procedures, EMEA procedures)

IR Investigator site

Basic Items

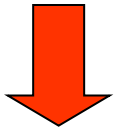
- Administrative information
- Reference texts and documents for the inspections
- Conduct of the trial
- Documents reviewed during the inspection, including a summary of the SDV conducted
- Accountability of medicinal products
- Laboratories, technical departments
- Monitoring and auditing
- GCP compliance, summary and conclusion
- Dates and signatures of inspectors

IR Sponsor site

Basic items

- Administrative information
- Reference texts and documents for the inspections
- Sponsor system inspection
  - -organisation and personnel
  - -facilities and equipment
  - -SOPs
  - -QA
  - -monitoring
  - -IMP management
  - -data management
  - -CTs pharmacovigilance
- GCP compliance, summary and conclusion
  - Dates and signatures of inspectors

NON-COMPLIANCE



FINDINGS

Critical, Major, Minor

Each deviation or at least for critical and major findings should refer to the requirements for which it is non-compliant (legislation, guidelines, trial protocol)

Critical finding:

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.

from the EMEA SOP INS/GCP/4

Major finding:
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 principles.

Possible consequences: data may be rejected and/or legal action required

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

Minor finding:

Conditions, practices or processes that would not be expected to adversely affect the rights, 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, practises and processes.

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

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

An IR is defined as complete when the inspectors have assessed the responses from the inspectees on the findings described in the original IR

Inspection report-For whom?

Within a Members State

according to national regulations and procedures

-Inspectees

-Sponsor/CRO

-Courts/other authorities (if required)

-MA applicant

GCP Inspection Findings

- Protocol adherence
  - Failure to respect eligibility criteria
  - Failure to adhere to protocol (IMP dosage, technical and/or laboratory procedure, visit range)
- Data recording
  - Fraud: patient does not exist, test not performed, one ECG for all the patients in BE studies, chromatograms built at PC
  - Misconduct: no source documents,
    dates and events do not match,
    correcting fluid used to cover source data

GCP Inspection Findings

- Contract Management
  - Absence of formal agreements
  - Omissions, errors and discrepancies in contracts/agreements
  - Responsibilities of collaborating parties not clearly defined
  - Many activities delegated to Principal Investigator without agreements

- Informed Consent
  - No records of consent being taken
  - IC obtained after the trail starts
  - Inconsistencies with protocol/amendments
  - Inadequate/incorrect form used
  - Inadequate language version
  - Investigator do not know the local language

GCP Inspection Findings

- Pharmacovigilance
  - Lack of awareness of legislative requirements (7 and 15 day reports)
  - Failure to distinguish AEs and ADRs
  - Failure to identify ‘Serious events’
  - Failure to consider event expectedness, and hence to identify events which require IMMEDIATE reporting
  - Lack of involvement of Principal Investigator
  - Failure to monitor pregnancy to outcome
  - Failure to monitor increased severity or frequency through trend analysis

GCP Inspection Findings

- Contacts with ECs or authorities
  - Provisional approval not fulfilled
  - Failure to notify EC and RA of changes
  - EC inadequate constitutions
  - Failure to notify EC and RA of end of trial

GCP Inspection Findings

- Quality control
  - Inadequate monitoring
  - Monitor without GCP/protocol training
  - Monitor reports contain no information
  - No follow up actions
- Miscellaneous Findings
  - Lack of GCP training or evidence of training, inadequate CV
  - Study documentation storage insecure or inadequate retention periods
  - Insurance expired

GCP Inspection Findings

- Investigational Medicinal Product

  - Labelling not compliant with GMP Annex 13
  - Inadequate records to track the IMPs during the transport
  - Missing or unsigned documentation - accountability, dosing, shipping & no alternative mechanism to verify protocol compliance
  - Queries in underlying pharmacy systems & procedures e.g. action in the event of out of specification temperature storage
  - Failures in accountability - difficulty in determining who was dosed, when, and with what

GCP Inspection Findings

CT pharmacy

- No IMP shipment notes from the Sponsor
- IMP shipment notes without key elements
- No IMP internal shipment notes between investigator and pharmacy
- IMP delivery directly to the investigator
- IMP stored mixed with other drugs
- IMP storage without T° monitoring (when required)
- IMP storage at the wrong T°
- Local drug destruction without documentation/SOP

GCP Inspection Findings

Sponsor site

- Documentation
  - Failures in quality systems e.g.:
    - lack of approved, controlled, documented procedures (SOPs)
    - Uncontrolled documents used in place of SOPs
  - SOPs / Protocol do not reflect current practice or current legislation
  - Failure to keep pertinent and complete records: e.g. key meetings/decisions not documented, in-process checks not documented

GCP Inspection Findings

Sponsor site

- Miscellaneous findings
  - Computerised systems not validated
  - Inadequate training
  - No criteria to select third parties
  - No audit of third parties
  - Lack of clear definition of a protocol violation/deviation/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
  - Assessment of the relatedness of SAEs performed by the sponsor personnel, who did not have access to all available information concerning the IMP

Domande

Dott.ssa Angela Del Vecchio
Direttore Ufficio Ispezioni GCP
phone: 0039 06 5978 4357
email: a.delvecchio@aifa.gov.it