Role of Regulatory Authorities in GCP implementation

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Role of Regulatory Authority

- Application for clinical trial licence
  - Pre-clinical data
  - Clinical data
  - Investigational product
  - Protocol – risk benefit
- Pharmacovigilance
  - safety reporting
- Inspection
- Evaluation of results

Objectives of inspections

- Verification of patient safety and integrity
  - protection of patient who will or are participating in clinical trials
- Verification of data
  - protection of patients who will be treated with marketed medicinal products
- Adherence to laws and regulations
  - local and international
- Training and education

Compliance with GCP standard provides public assurance that

- the rights, safety and well-being of trial subjects are protected
- the clinical trial data are credible

Trial subject

- Declaration of Helsinki
- Ethics Committee approval
- Confidentiality
- Informed consent
- Medical care and decisions by qualified physician

Data

- Can we rely on the credibility of the data

- Application to Regulatory Authorities for permission to start clinical trails
- Clinical Trial Report
- Application to Regulatory Authorities to obtain registration (market authorization)

Regulatory framework

- Declaration of Helsinki
- GCP (ICH, WHO or other)
- Local laws and regulations
  - Clinical trial
  - Ethics
  - Medical care and records
  - Secrecy and confidentiality

Audits in guidelines/regulations

- FDA - No requirement
- ICH - If or when sponsors perform audits as part of implementing quality assurance
  - ICH GCP 5.19
- Local Requirement - ?

Audit versus Inspection

- Sponsor/CRO
- Focus on compliance and process review
- Against laws, regulations and sponsor SOPs
- Vested interest in ensuring study success

- Regulatory agency
- Patient safety and data credibility
- Sponsor SOPs usually irrelevant
- Study “success” irrelevant

Inspecting clinical trials

Inspecting can be :

- Diagnostic to determine room for improvement
- Evaluation to confirm or refute compliance
- Surgical to delete improper data to ensure credibility

Risk Assessment

- What is the best way to protect trial subjects and verify the quality of trial data? Given the limited inspection resources, some potential factors:
  - Target those sponsors/investigators that perform the most trials
  - Target trials that provide data for marketing authorisation applications
  - Target high risk trials (e.g. number of patients, type of patient population, safety issues, issues relating to the sponsor)
  - Target trials for which issues have been identified (Ethics Committee concerns, informants)

Intended outcome

- Improved quality
- By doing few achieve a lot
- Awareness by being seen
- Accepted as a source of information
- Appreciated by the pharmaceutical industry and academia
- Recognised by international society

Points to consider

- How many trials are conducted
- What types of trials are conducted
  - commercial/non-commercial
  - Early phase/late phase
  - Healthy volunteers/patients
  - Inclusion/non-inclusion of data in regulatory submission
- What oversight of these trials already occurs and by which government organisation

Points to consider

- What percentage of sponsors have offices in the country
- What resources would be required to address the agreed inspection strategy
- How will inspection be financed:
  - by sponsor, e.g. inspection fee, CT application fee
  - by marketing application authorisation holders
  - government funding

Points to consider

- What are the most efficient ways to protect trial subjects and verify the quality of the trial data with the available resource (risk assessment)
- How frequent might the organisation be asked to participate in international inspections (at home and abroad)
- What actions can be taken for GCP non-compliance?
- What are the expectations of stakeholders (patients, industry, government, academia)

Inspection strategy

- Focus on achieving quality into the process in ongoing studies rather than finding faults in completed studies
- Inspection part of training and education

Inspection strategy

- Focus on completed studies?
  - data driven
- Focus on ongoing studies?
  - process driven

- Inspection part of training and education

Inspection strategy

- Clinical sites
- At least once a year to all major pharmaceutical industries
- Small companies and academia ad hoc
- Networking with the academic organisations
- Education and training

Lessons learned

- Improved quality
- By doing few achieve a lot
  - cascade effect
- Awareness by being seen
  - small country – few players

Lessons learned

- Accepted as a source of information
  - readily available
  - frequent contacts
- Appreciated by the pharmaceutical industry and academia
  - well-known and respected
  - communication and transparency

Objectives

- To develop a system for GCP inspection in respective country that ensures that inspections are:

  - conducted according to international standard
  - recognised as acceptable by the international society
  - conducted by qualified inspectors

System and procedures

Harmonisation and expertise through practical action and communication

- Implement standard policy and procedures
- Share experience; harmonize grading of findings; inspection reports
- Shared inspections
- Exchange of information
- Training

To be considered on a national and international level

System and procedures

Implementation of Standard Operating Procedures

- Preparation of inspections
- Reporting of inspections, including grading of findings
- Conduct of inspection
- Inspection records
- Sponsor/CRO, investigator/laboratory
- Pharmacovigilance
- Computer systems
- Phase I sites/Bioequivalence inspection
- Ethics Committees
- Investigational Medicinal Products

http://www.emea.europa.eu/Inspections/GCPproc.html

- INS-GCP-1 Procedure for coordinating GCP inspections requested by the EMEA Corr.
- INS-GCP-2 Procedure for preparing GCP inspections requested by the EMEA
- INS-GCP-3 Procedure for conducting GCP inspections requested by the EMEA
- INS-GCP-3 Annex I to Procedure for conducting GCP inspections requested by the EMEA- Investigator Site
- INS-GCP-3 Annex II to Procedure for conducting GCP inspection requested by the EMEA- Clinical Laboratories
- INS-GCP-3 Annex III to Procedure for conducting GCP inspection requested by the EMEA- Computer Systems Rev. 1
- INS-GCP-3 Annex IV to Procedure for conducting GCP inspections requested by the EMEA- Sponsor and CRO
- INS-GCP-3 Annex V to Procedure for conducting GCP inspections requested by the EMEA- Phase I Units
- INS-GCP-3 Annex VI to Procedure for conducting GCP inspections - File structure and archiving
- INS-GCP-4 Procedure for reporting of GCP inspections requested by the EMEA
- Principal Documents taken into account for the preparation of procedures for the GCP inspections requested by the EMEA

Inspection procedures

- Inspection made to suit inspection site/inspectees
- Different circumstances may require a different approach but all based on:
  - same set of legal requirements
  - same set of inspection activities
  - same set of inspection SOPs
  - inspection team: made to measure
  - fitted to regulatory environment

Types of inspections

- **for-cause inspection**
  - indication that something is not optimal in the study
  - the suggestions can come from
    - Regulatory Authority
    - Sponsor company
    - Head of Clinic or other staff at the clinic
- **routine inspection**
  - randomly picked clinical trials for inspection

Objects of inspections

- **Individual studies**
  - investigator
  - sponsor
  - CRO
- **System inspections**
  - sponsor
  - clinical trial center
  - CRO

Objects for inspections

- Sponsor
- CRO (various sites)
- Investigator
- Pharmacy
- Laboratory (special departments)
- Manufacturer, vendor
- Archives
- Ethics Committee

Objects of inspections

- **Pharmacovigilance inspections**
- **Bioequivalence/bioavailability**

Objects of inspections

- **All types of studies**
  - phase I-IV
  - academic or company sponsored
- **When**
  - ongoing studies
  - after completion

Inspection Goal

- A positive educational experience for Investigator, staff and sponsor personnel

Certification of inspectors

- Training in laws and regulations
  - local
  - International
- Training in other disciplines
  - GMP, GLP, GPP, GDP
- Internal instructions (SOPs), reporting, behavioural etc.

Certification of inspectors

- Appoint appropriately qualified inspectors
  - background education
    - Pharmacists, M.Sc., MD etc.
  - practical experience
    - pharmaceutical industry, clinical trials
  - personality
    - policeman or negotiator
  - language
    - international communication

Inspector characteristics

- Honesty
- Open-minded
- Interpersonal skills
- Professional skills
- Disciplined approach
- Proactive
- Leadership

Non-Inspector characteristics

- Aggressive
- Intimidating
- Stubborn
- Sneaky
- Uncooperative
- Nit picking

Certification of inspectors

- Standardized certification programme
  - depending on background but at least 6-12 months
- Participation in inspections in the country
  - observer
  - participant
  - leader

Certification of inspectors

- Develop an international inspection programme in collaboration with:
  - EMEA
  - FDA
  - WHO
  - Other relevant authorities