Federal Agency for Medicines and Health Products

GCP Compliance

KCE

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A. ICH-GCP E6

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References

- « ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95
- ICH-E3, ICH-E9 guidelines
- 2001/20/EC and 2005/28/EC directives
- Loi du 7 mai 2004 relative aux expérimentations sur la personne humaine, modifiée par la loi programme du 27 décembre 2004 ;
- Arrêté royal du 30 juin 2004, modifié par l'arrêté royal du 18 mai 2006 déterminant les mesures d'exécution de la loi du 7 mai 2004 ;
- Arrêté royal du 14 décembre 2006 concernant les médicaments à usage humain et vétérinaire

Definition

Who are responsible for GCP

- **The responsibilities for GCP are shared by all of the parties involved in CT, namely :**
  - **Sponsors**
  - **Investigators and site staff**
  - **Contract Research Organizations (CROs)**
  - **Ethics Committees**
  - **Regulatory Authorities**
  - **Research subjects**

Definition

Which parts are covered by GCP :

1. Ethics Committee/Independent Review Board
2. Investigators
3. Sponsors
4. Protocols
5. Investigator's Brochure (IB)
6. Essential documents

Definition :

following GCP ICH-E6 & Law 7/05/2004 Art 2.

Investigator : A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Sponsor : An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Principles

Which are the great principles of GCP ?

- **Ethics**

1. Ethical conduct of CTs (following the declaration of Helsinki)
2. The benefits justify the risks
3. Rights, safety and well being of subjects prevail over all

- **Protocol and science**

4. Non-clinical and clinical information supports the trial
5. Compliance with a scientifically sound, detailed protocol 💣

- **Responsibilities**

6. IEC/IRB approval mandatory prior to initiation
7. Medical care and decisions should always been taken by (a) qualified physician(s) 💣
8. Each individual involved in conducting a trial should be qualified by education/experience/training 💣

Principles

Which are the great principles of GCP ?

- **Informed consent**

9. Freely given ICF from every subject (and/or legal representatives) prior to participation 💣

- **Data quality and integrity**

10. Accurate reporting, interpretation and verification of the CT data and information 💣

11. Protection of the confidentiality of the records

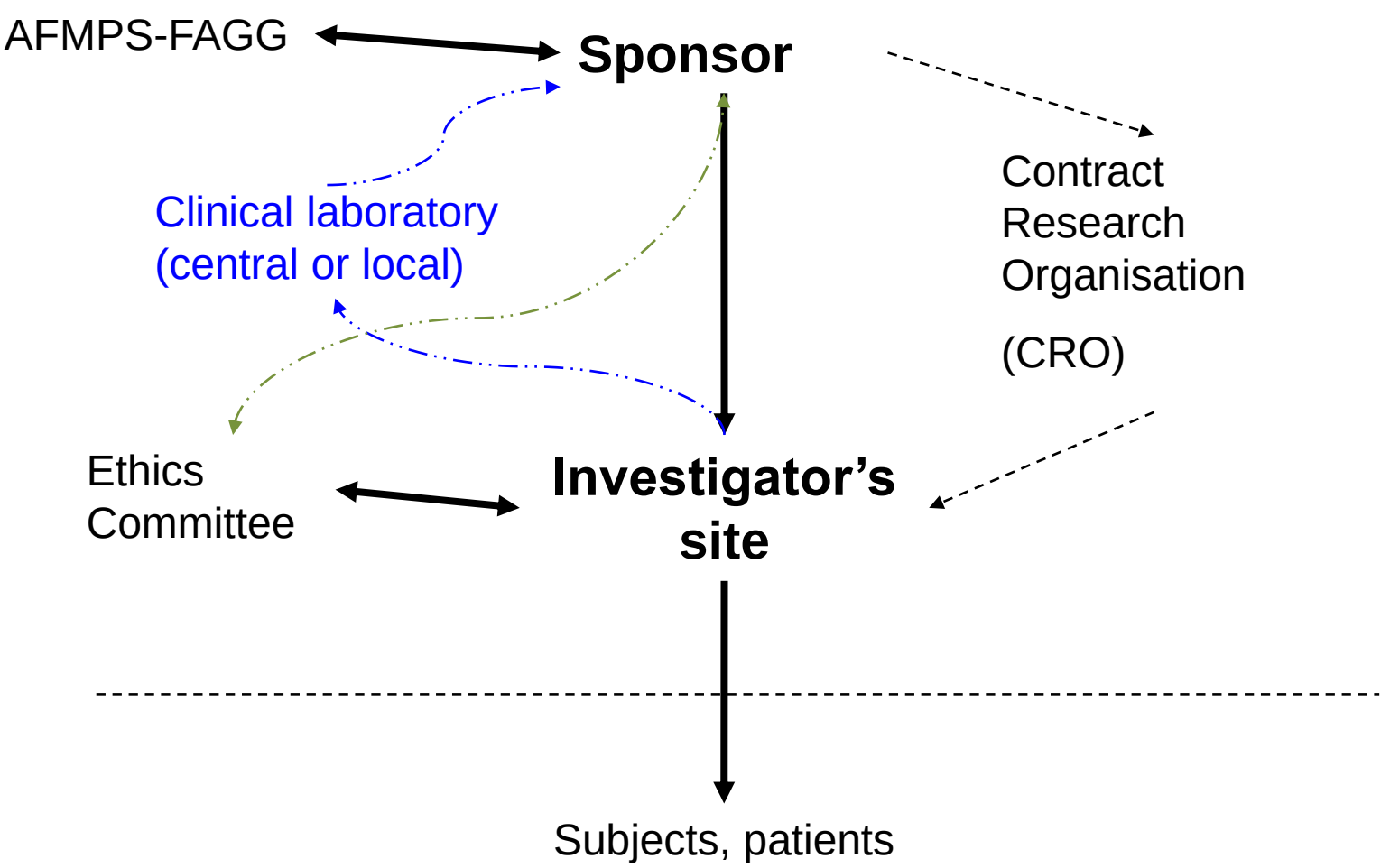
- **Investigational products**

12. Conform to GMP's and used per protocol

- **Quality control/Quality Assurance**

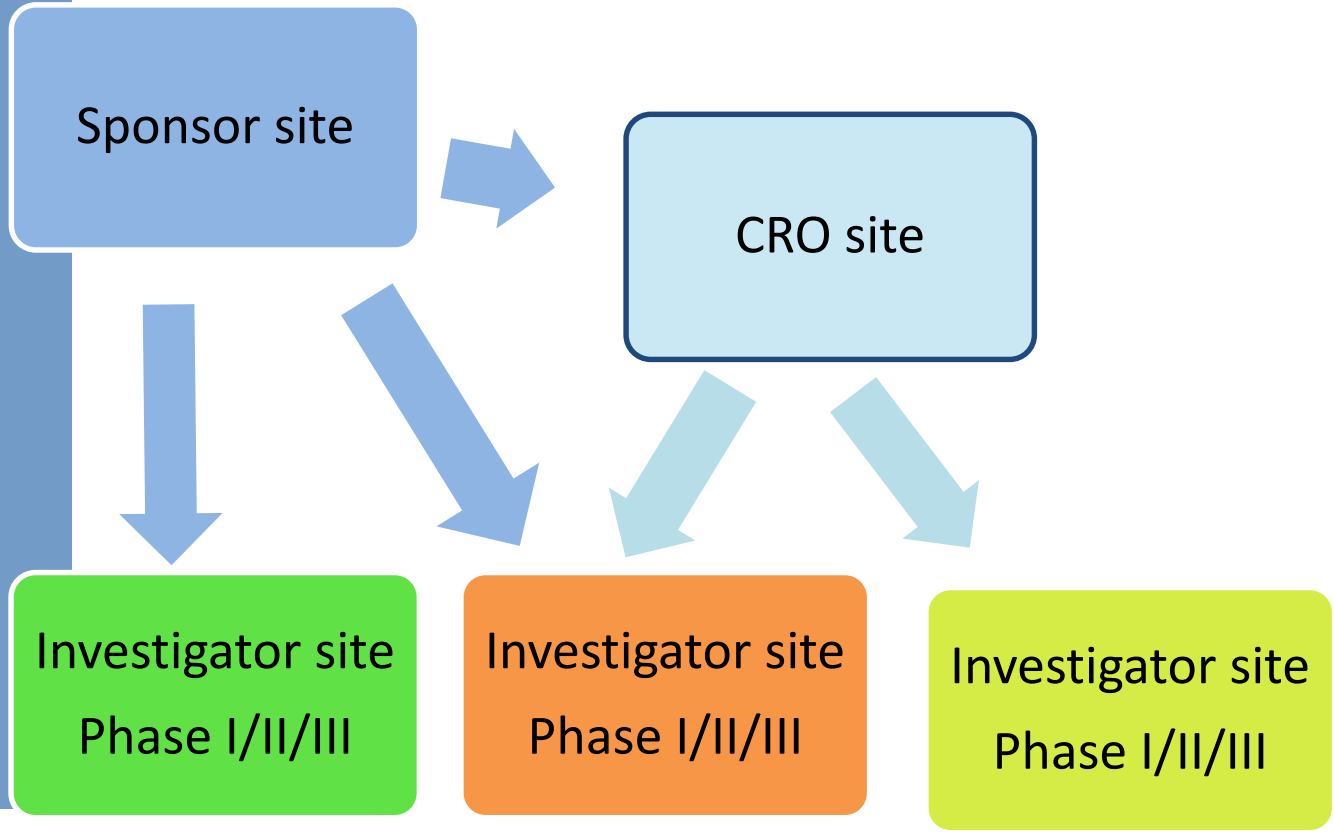
13. Systems with procedures to ensure quality of every aspect of the trial should be implemented 💣

Actors involved in Clinical Trials



Type of Sites to inspect

List of sites or involved parties to inspect in the CT process



- Phase I unit
- Laboratories
- Bioequivalence unit
- Monitoring/ Data Management/ Statistics
- IMP management/ shipment & distribution
- Pharmacy
- Etc…

Investigator site

Investigator team :

Principal Investigator (PI)
+ Sub-Investigator(s)

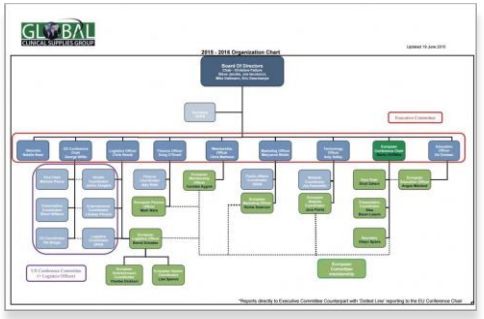
- Study Nurses
- Clinical research coordinator
- Data manager

Data,
information

- Information, care, IMP
- Protocol

Subjects ⇔Patients

Sponsor site



A. Introduction

- 2 main types of inspection for the sponsor site :
- This can be related to a specific trial, a specific study, a specific protocol

➢ Specific Inspection

- This can be related to one or several processes led by the sponsor like Data Management, QMS, Monitoring, Statistics, CT preparation and implementation, IMP distribution, …)

➢ Systemic Inspection

- An inspection of a CRO often follows the same inspection procedures and points as for a sponsor site inspection.

Sponsor site

At the sponsor site, the GCP focuses on :

1. Quality Assurance & Quality Control
2. CRO
3. Medical expertise
4. Trial Design
5. Trial Management, Data Handling & Record Keeping
6. Investigator Selection
7. Allocation of Responsibilities
8. Compensation to subjects and investigators
9. Financing
10. Notification/submission to RA
11. Confirmation of Review by IRB/IEC

Sponsor site

At the sponsor site, the GCP focuses on :

12. Information on Investigational Product(s)
13. Manufacturing, Packaging, Labelling and Coding IMP
14. Supplying and Handling IMP
15. Record Access
16. Safety information
17. Adverse Drug Reaction Reporting
18. Monitoring
19. Audit
20. Noncompliance
21. Premature termination or suspension of a trial
22. Clinical Trial/ Study reports
23. Multicentre trials

Sponsor sites : systemic inspection scope

Following the annex IV to the procedure for conducting a GCP inspection for sponsor and CRO site, several main topics must be inspected following a systemic point of view :

A. Sponsor or CRO Quality System Inspection

- **I. Organisation & Personnel**
- **II. Facilities and equipment**
- **III. SOPs**
- **IV. Implementation & termination of a trial**
- **V. Monitoring Activities**
- **VI. IMP**
- **VII. Safety and AE reporting**
- **VIII. Data handling and Clinical Study Report**
- **IX. Documentation archiving**
- **X. Sponsor audit and QA system**
- **XI. Delegation of duties**

Sponsor sites : specific inspection scope

Following the annex IV to the procedure for conducting a GCP inspection for sponsor and CRO site, several main topics must be inspected following a specific point of view :

All the previous points of a systemic scope must be inspected but for a trial, those points have to be inspected according to the study concerned by the inspection and particularly the data (efficacy, safety, IMP, labs, ...) reported to the sponsor in the CSR and some points related like :

- **IMP accountability, IXRS, randomization, blinding**
- **Monitoring and trial management in the details**
- **Data Management, Source Data Verification, CRF data verification and management**
- **SAEs management and reconciliation**
- **Statistics and CSR writing**
- **TMF and Archiving**

CROs

- **CROs are inspected following the method and organization of a sponsor inspection, however some CROs are specialized :**
  - **IMP distribution**
  - **IXRS system (Integrated phone and web IMP management)**
  - **Image reading specialized CRO**
  - **Central laboratories**
  - **CRO specialized in EDC, Data management and/or statistics**
  - **…**
- **For each of those CROs, the inspector must adapt his inspection and be at least aware, but not necessarily an expert, of those matters.**

ICH-GCP E6 :
Protocol and Investigator's Brochure

- **ICH GCP E6 also defines, in the part 6, all the sections requested to write a protocol following the GCP**

- **ICH GCP E6 advises, in the part 7, how to set or update the sections needed in the IB**

TMF : essential documents GCP point 8

Essential documents: ALL documents related to the trial in compliance with the principles and guidelines of GCP. They must allow us to fully reconstruct the trial data and events :

- **Generated from organisations procedures**
- **Not restricted to ICH GCP section 8.**

Those documents are divided in 3 parts : before the trial starts, during the conduct of the trial and documents belonging to the end of the trial.

TMF : essential documents GCP point 8

It includes : IBs, protocol and amendments, agreements/contracts, insurance statements, EC and RA approvals, CV and training form, lab documents, instructions for IMP, decoding procedures (unblinding), randomization list, source documents, CRF, IMP accountability, signed ICFs, monitoring reports, subjects logs, delegation log, …

A specific part of those documents are either part of the SMF in the investigator site or either part of the TMF in the sponsor site. Therefore some documents belongs mandatory to the PI, others to the sponsor. Some belongs to both.

Main findings observed at sponsor site following GCP inspections

Sponsor Site : Quality Management System, Protocol-IB-ICF design, Data Management, CT Supervision and Management, Communication with EC and CA, Safety reporting, Monitoring, Audit, TMF administration and organization

GCP Inspection : Conclusions

1. **Following our experience, the GCP quality of the clinical studies in Belgium are pretty good. It's an asset to keep and to improve !**

2. **GCP is not an administrative burden when it is smartly applied. If GCP is organized and thought as an integral part of the CTs from the start then « the burden » is lowered, the quality of the ethical and safety process is enhanced and the data (efficacy or safety) are compliant with the best standards of quality.**

Never forget that at the end, GCP is related with the quality of the validation of CSR supporting Evidence Based Medicine.

We as inspectors are not only « policemen » of the quality but also we try to help improving quality of CT « GCP facilitators ».

Basic Interesting internet links for GCP

Good Clinical Compliance EMA (GCP Insp WG)

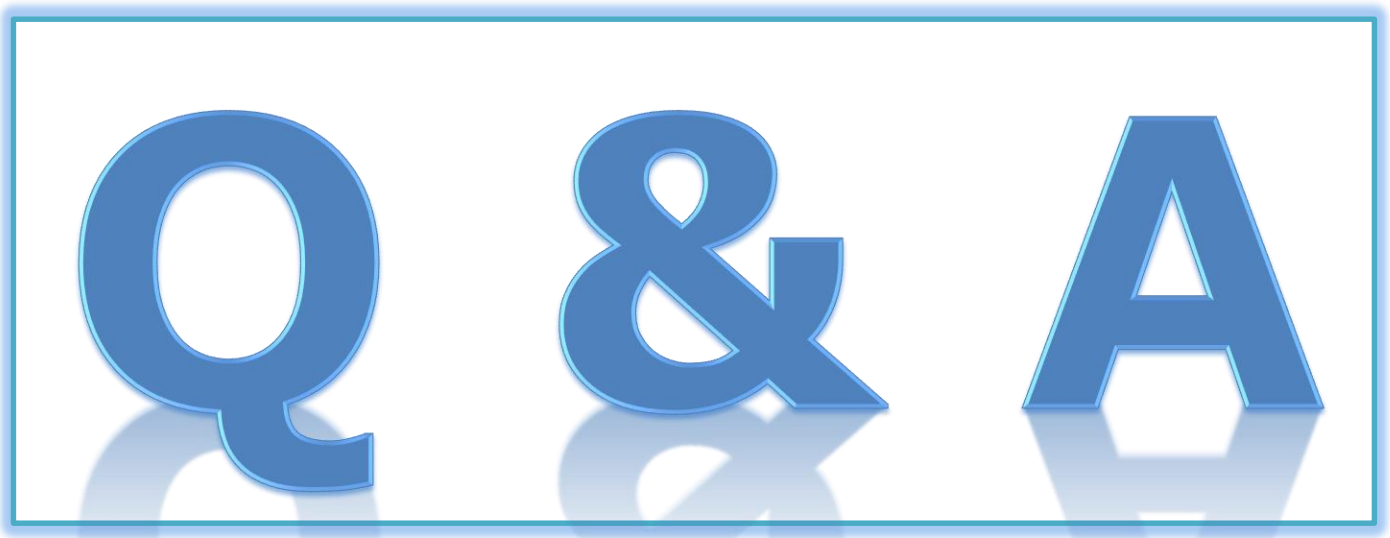
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000072.jsp&mid=WC0b01ac05800268ad

Volume 10 EudraLex

http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

ICH Efficacy guidelines

http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html


Q & A

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