Quality Assurance in Clinical Trials

Doctor Catherine CORNU, Lyon clinical Investigation Centre
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Introduction: quality in clinical research in human subjects

Regulatory requirements:

- “GCP”: GUIDELINE FOR GOOD CLINICAL PRACTICE (ICH Harmonised Tripartite Guideline)
- Directive 2001/20/EC of 4 April 2001 relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- National laws
- Others (e.g. CONSORT ....)

= Reference texts for QA
GCP: definition

- ethical and scientific **quality standard** for trials.
- provides public assurance that
  - the rights, safety and well-being of trial subjects are protected,
  - and the clinical trial data are credible.
- objective: to provide a unified standard for the European Union (EU), Japan and the United States to facilitate mutual acceptance of clinical data by the regulatory authorities.
- for clinical trial intended to be submitted to regulatory authorities … may also be applied to other clinical investigations
GCP: contents

1. Glossary
2. The Principles of ICH GCP
3. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
4. Investigator
5. Sponsor
6. Clinical trial protocol and protocol amendment(s)
7. Investigator’s brochure
8. Essential documents for the conduct of a clinical trial
GCP: glossary

Examples:

- **Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

- **Quality Control (QC):** The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.
GCP: principles

- Respect of ethical principles / regulatory requirement(s).
- Justified risks and inconveniences / anticipated benefit
- Subject rights, safety, well-being prevail over science / society.
- Nonclinical and clinical data justify the clinical trial.
- Detailed protocol scientifically sound
- Respect of protocol approved by IRB / IEC.
- Qualified physician, persons (education, training, experience).
- Free and informed consent
- Data recording, handling, and storage allows accurate reporting, interpretation and verification.
- Confidentiality (respect of privacy)
- Respect of good manufacturing practice (GMP).
- Procedures to assure the quality of every aspect of the trial.
Responsibilities: safeguard the subjects’ rights, safety; special attention for vulnerable subjects.

Composition, Functions and Operations:

- At least: 5 members,
- one nonscientific member,
- one member who is independent of the institution/trial site.

Procedures

Records
INVESTIGATOR

- Qualifications and Agreements
- Adequate Resources
- Medical Care of Trial Subjects
- Communication with IRB/IEC
- Compliance with Protocol
- Investigational Product(s)
- Randomization Procedures and Unblinding
- Informed Consent of Trial Subjects
- Records and Reports
- Progress Reports
- Safety Reporting
- Premature Termination or Suspension of a Trial
- Final Report(s) by Investigator
SPONSOR (1)

- Quality Assurance and Quality Control
- Contract Research Organization (CRO)
- Medical Expertise
- Trial Design
- Trial Management, Data Handling, and Record Keeping
- Investigator Selection
- Allocation of Responsibilities
- Compensation to Subjects and Investigators
- Financing
- Notification/Submission to Regulatory Authority(ies)
- Confirmation of Review by IRB/IEC
SPONSOR (2)

- Information on Investigational Product(s)
- Manufacturing, Packaging, Labelling, and Coding
- Investigational Product(s)
- Supplying and Handling Investigational Product(s)
- Record Access
- Safety Information
- Adverse Drug Reaction Reporting
- Monitoring
- Audit / Noncompliance
- Premature Termination or Suspension of a Trial
- Clinical Trial/Study Reports
- Multicentre Trials
CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

- General Information
- Background Information
- Trial Objectives and Purpose / Trial Design
- Selection and Withdrawal of Subjects / Treatment of Subjects
- Assessment of Efficacy / Assessment of Safety / Statistics
- Direct Access to Source Data/Documents
- Quality Control and Quality Assurance
- Ethics
- Data Handling and Record Keeping
- Financing and Insurance
- Publication Policy
- Supplements
INVESTIGATOR’S BROCHURE

- a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects.

General Considerations

Contents of the Investigator’s Brochure

- aim: to provide a clear understanding of possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial.
“Trial master files”

1) before the trial commences,
2) during the clinical conduct of the trial,
3) after completion or termination of the trial.
Quality in clinical trials: practical aspects

Quality Assurance in a clinical trial Unit, example: Lyon Clinical Investigation Centre

Scope:
- interventional clinical trials
- Sponsored by Industry / academia / charity
- From protocol design to final report / publication

CICs are not sponsor they act on behalf of sponsors (academic or industry)
structure description: cartography
Quality Management - Definitions

- Quality = Ability of a system to meet customers needs and applicable regulatory requirements
- Identifies and meets the needs and expectations of other parties (e.g. employees, suppliers, owners)
- Achieves competitive advantage in an effective manner
- Maintains and improves overall performance and capabilities
Quality Management – Definitions 2

Quality management:

- Coordinated actions to ensure quality and to control Quality
- It includes:
  - Quality Policy and objectives defined by the head of the Unit
  - Techniques and activities to garanty quality
Identify needs of customers

- Customers: patients, investigators, sponsors, hospital, INSERM directors, Editors of Biomedical Journals

- Documents:
  - Laws
  - Study specific documents: protocol, contract, SOPs
  - Other referentials: guidelines and recommendations (ICH, clinical practice recommendations: health authorities, scientific societies, CONSORT and associated guidelines)
Collaborators of the CIC

TUTELLES
INSERM
DGOS (CHU)

COLLABORATEURS
Services hospitaliers collaborant
Centres de Ressource Biologique
Unités EPST : INSERM, CNRS, INRA
Unités de productions : UTCG et EFS
Prestataires
Unités de Recherches Cliniques

CLIENTS
Promoteurs Industriels
Promoteurs institutionnels
Investigateurs

BENEFICIAIRES
Participants sains
Participants malades
QA: an evolving process

- Identify needs, update
- Define objectives: e.g. shorten time intervals, improve conformity of practices to Procedures: presence of patient card, use of templates for protocols, CRFs
- Evaluate the quality: indicators
  - rate of patient accrual,
  - rate of withdrawal
  - Ethics Committee acceptance at first submission
- Evaluate the quality: means: internal audits, working group, direction review meetings
- Improve quality
Quality documentation

→ a tool in the direction of all employees to live and grow with the quality system itself.

A quality system documentation → based on a feedback loop that generates and combines documents, reports and record corrective and preventive actions.
QA system: organisation, procedures, processes and means implemented for QA

- Policy / Objectives: Quality manual / unit organisation
- SOPs
- Instructions, check lists, forms, templates
- Tracing documents
QA system

- Commitment of the Head of the Unit
- Training of the staff
- Documentation of the Quality: quality manual
- Processes
- Continuous assessment / improvement
Examples of objectives for next year

- Training for the staff to ….
- Conformity check lists: protocol, patient information / consent sheets
- GCP qualification of the staff
- Biological samples: handling, transport, storage
Examples of training for the team

- Initial training: CRA training / documentation: CV
- Continuous training: documentation (attendance sheet)
  - Internal meetings: example of topics: data management: means to implement to get alerts for inclusions, SAEs
  - Follow-up of quality indicators
  - Attendance to university teaching
  - Sponsor training for each study
  - Update training on regulatory
Examples of training for the team

- Habilitations:
  - Biological sample management
  - Site visits
- Attendance to meetings for continuous education
Quality manual

- Commitment of the Head
- Design a QA responsible, time devoted to QA
- Describes the QA system, QA policy
- Describes the organisation: organigrams, function definitions, QA system, processes, refers to SOPs, registration documents

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QA system: organisation, procedures, processes and means implemented for QA

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What is a SOP?

Standard Operating Procedure
A SOP is a set of written instructions that describes a routine or repetitive activity.

SOPs:
- Describe both technical and administrative operational elements of an organization
- Require to be managed under a Quality Assurance Project Plan and a Quality Management Plan
A SOP should

- ensure ease and efficiency in use
- be specific to the organization that develops it.

There is no one 'correct' format → internal formatting varies within each organization
How much detail needs to be included in a SOP?

A SOP should be written with sufficient details to allow someone with basic understanding to successfully reproduce the activity.
What is the benefit of having a SOP?

- Development and **use** of SOPs is an integral part of a successful quality system.
- Provides individuals with information to perform a job properly.
- Facilitates consistency in the quality and integrity of a product or end-result.
- Can also be used as a part of a personal **training** program.
- In addition, SOPs are frequently used as checklists by inspectors when auditing procedures.
Who should write a SOP?

- individuals that are subject-matter experts
- who actually perform the work or use the process.
- A team approach for multi-tasked processes.
- Lyon CIC:
  - 2 field persons (one writer), one supervisor
  - Validation by clinical research physician
To write a SOP

SOPs describe the sequence of steps that forms a process. For each step, you must define:

- Input (materials, information, …)
- The transformation actions (who, what and how)
- Output

Should be understandable by all.


To write a SOP (Content, example)

- **Purpose**: in few lines why the procedure
- **Scope**: "Where and when will you use this procedure?"
- **Skills**: to describe the responsibility of each person involved in the process
- **Definitions – Terminology – Abbreviations**: to explain the words, symbols used in this procedure
- **Modality of implementation**: to draw a step by step guide or a flow chart
- **Associated documents**: to list all applicable regulatory documentation, all linked procedures
Flowchart symbols

- 1st or last step
- Step or action
- Link
- Document link to a step
- Check
- Decision / choice
- Storage / Archiving
- Delay

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Example list of **procedures**

<table>
<thead>
<tr>
<th>Code</th>
<th>Procédure</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCT-001</td>
<td>Gestion des documents Assurance Qualité</td>
</tr>
<tr>
<td>FCT-008</td>
<td>Gestion des situations d'urgence</td>
</tr>
<tr>
<td>FCT-029</td>
<td>Bilan d'activité</td>
</tr>
<tr>
<td>FCT-031</td>
<td>Bilan financier</td>
</tr>
<tr>
<td>FCT-034</td>
<td>Audit de système</td>
</tr>
<tr>
<td>FCT-036</td>
<td>Audit interne d'un essai clinique</td>
</tr>
<tr>
<td>FCT-039</td>
<td>Gestion de l'Information</td>
</tr>
<tr>
<td>FCT-044</td>
<td>Gestion docs dans Commun</td>
</tr>
<tr>
<td>FCT-046</td>
<td>Sauvegarde de la messagerie informatique</td>
</tr>
<tr>
<td>FCT-047</td>
<td>Recrutement au CIC</td>
</tr>
<tr>
<td>FCT-049</td>
<td>Présence médicale au CIC</td>
</tr>
<tr>
<td>FCT-050</td>
<td>Gestion des déplacements</td>
</tr>
<tr>
<td>FCT-051</td>
<td>Gestion de l'équipement</td>
</tr>
<tr>
<td>FCT-203</td>
<td>Commande Achats, Commandes et Prestataires</td>
</tr>
<tr>
<td>FCT-221</td>
<td>Organisation d'une réunion</td>
</tr>
<tr>
<td>FCT-238</td>
<td>Gestion nouvel arrivant</td>
</tr>
<tr>
<td>FCT-259</td>
<td>Gestion temps de travail personnel CIC</td>
</tr>
<tr>
<td>PRJ-052</td>
<td>Rédaction d'un devis</td>
</tr>
<tr>
<td>PRJ-057</td>
<td>Prise en charge d'un projet par le CIC</td>
</tr>
<tr>
<td>PRJ-059</td>
<td>Rédaction d'un protocole</td>
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<tr>
<td>PRJ-061</td>
<td>Demande promotion HCL</td>
</tr>
<tr>
<td>PRJ-075</td>
<td>Soumission d'un protocole au CPP</td>
</tr>
<tr>
<td>PRJ-101</td>
<td>Visite de mise en place</td>
</tr>
<tr>
<td>PRJ-103</td>
<td>Visite de monitorage</td>
</tr>
</tbody>
</table>
QA system: organisation, procedures, processes and means implemented for QA

- Policy / Objectives: Quality manual / unit organisation
- SOPs
- Instructions, check lists, forms, templates
- Tracing documents
Conclusion: QA in a public trial unit

- Same reference documents as industry / CRO
- (too) Few personnel, (too) few time devoted to QA
- Identify priorities
- Harmonisation is ongoing