QUALITY
IN CLINICAL RESEARCH

GCP

an International Ethical and Scientific quality standard by which clinical trials are designed, implemented and reported so that there is public assurance that the data are credible and the rights, safety, integrity and confidentiality of the subjects are protected

GCP

quality standard

that the data are credible

and the rights, safety, integrity and confidentiality of the subjects are protected

HOW ???

QUALITY IS:

- **SAY HOW WE PERFORM**
- **PERFORM AS WE SAID**
- **DOCUMENT WHEN WE DID NOT/ARE NOT PERFORMING AS SAID**
- **CHECK THAT WE HAVE PERFORMED CORRECTLY**

WHY ? ? ?

Why do clinical research companies bother so much ??

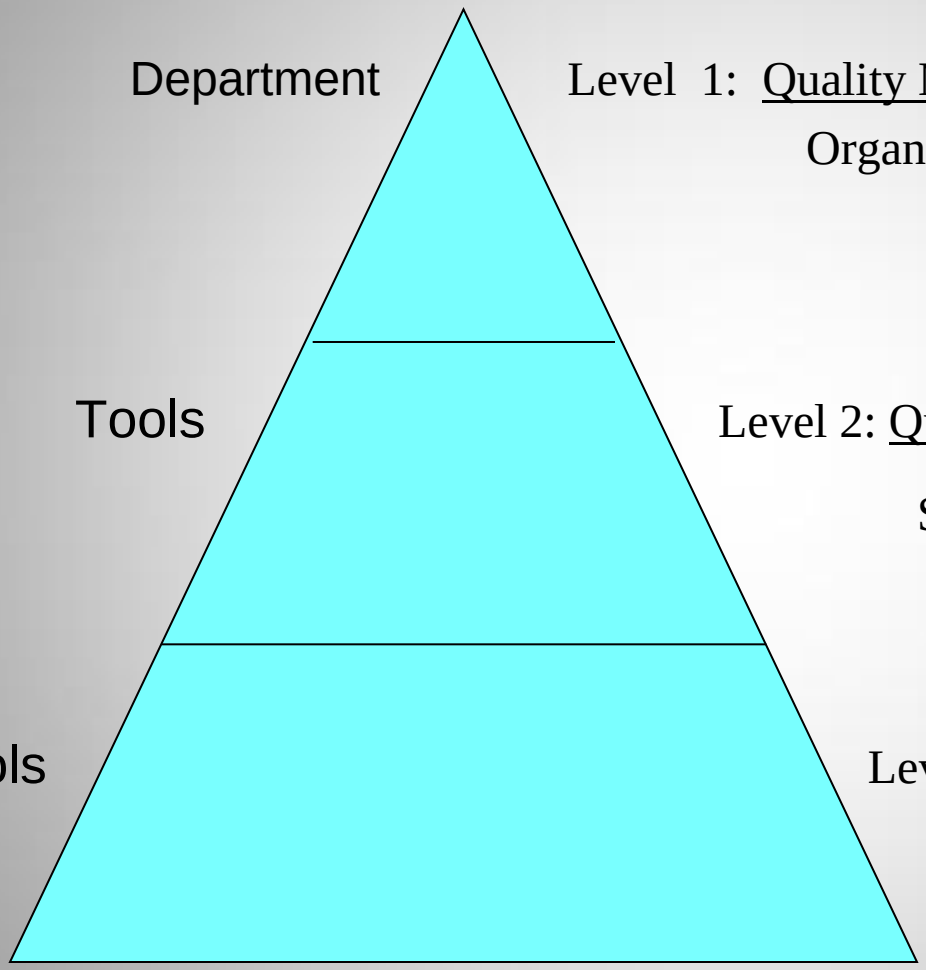
Inspectors

Auditors

Quality may be a burden

But it is the best tranquilizer ever invented

SAY HOW WE PERFORM



Level 1: Quality Management system

Organization and functions

Level 2: Quality Operating Documents : SOPs

Standard Operating Procedures

Level 3: Quality Working Documents

Forms – Templates

ORGANIZATION

Organization chart - description

Should be independent from operation & technical teams

Who does what : Quality sub-units (Clinical QA, Mfkg QA, IT QA,..)

Quality Target in terms of achievement

Regular Quality reporting to Top Management

Subcontractors

FUNCTIONS

Quality Assurance

Quality Control

QUALITY CONTROL and AUDITS

- QC and Audits organisation/schedule,..
- Decision flow (decision for QC, for quality issues, ..)
- Quality achievements: Indicators, CAPA post QC/audits

QUALITY ASSURANCE

PREVIOUS FIELD EXPERIENCE

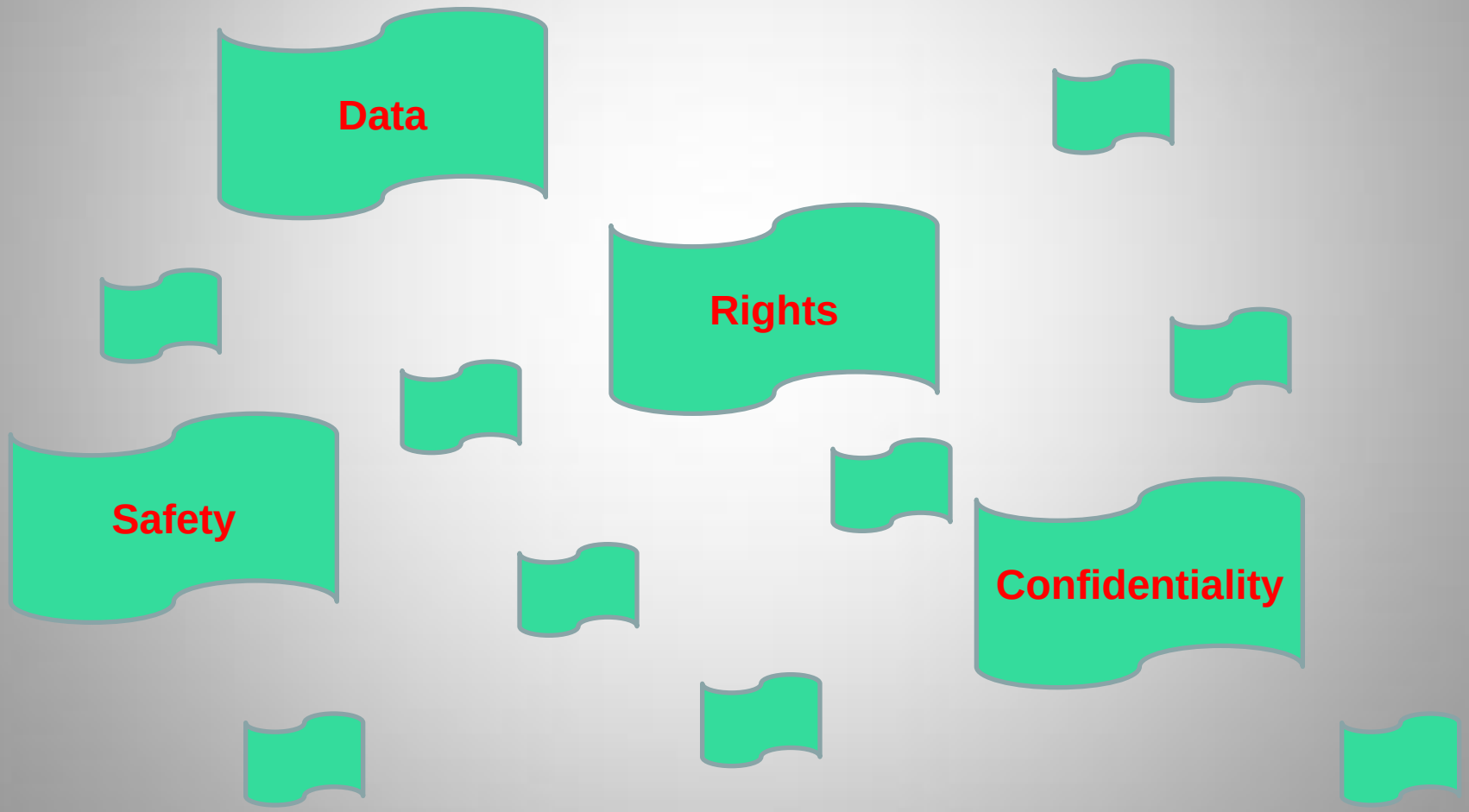
REGULATIONS FOLLOW-UP

A system should be in place for regulations & guidance follow up

Lead to establish the rules to be followed

The rules apply to : Work performance, Facilities and equipments

Work Performance : 95% of clinical research work



Installations : building plan, security, precautions..

(phase I facilities, badge/door key,.)

Equipments : equipment reliability, testing, validation, failure management

*** Alarm systems**

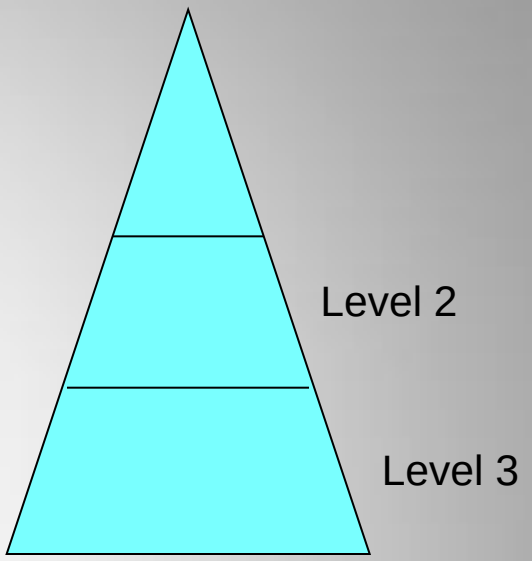
(computer system validation, lab storage,..)

RULES ARE HANDLED WITHIN A QUALITY DOCUMENTATION SYSTEM

QUALITY DOCUMENTATION SYSTEM

Issuing documents on:

- ❑ **The rules to be applied** →
- ❑ **How to apply the rules** →



By means of

- ➢ **Standard Operating Procedures**
  and
- ➢ **Working Documents**

What is the source of the rule, the SOP ??

What is the source of a Working document ??

GCP

"The investigator delegates …., but remains responsible"

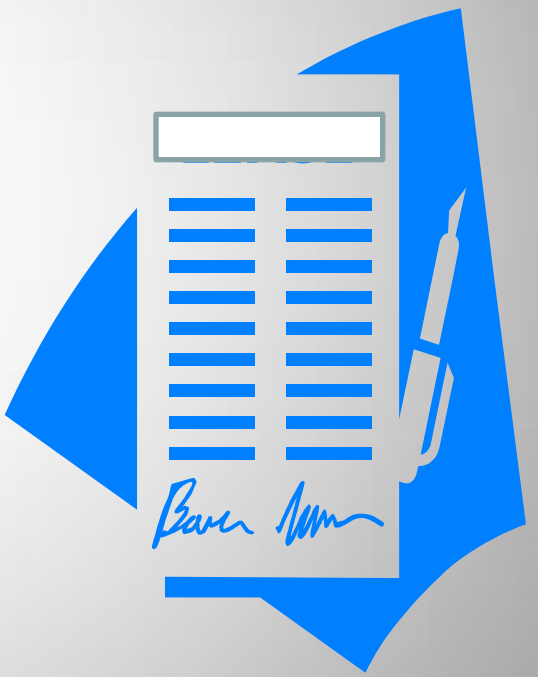
SOP

"The investigator delegation log should be collected"

SOP

« investigator delegation log should be collected “

Form: Delegation log



WHY

Standard Operating Procedures

?

WHY

Standard Operating Procedures

?

Operating (written) procedure

- How operations should be done : who, when, where
- Covers all operations required by regulations (no risk for missing an item) – Maximum compliance
- shown to auditors/inspectors
- retrieving past information

Standard Operating procedure

- All persons work in the same way
- Allows hand over
- Allows building related activities, softwares

STANDARD OPERATING PROCEDURE

- **Format et presentation**

Fixed template: Title, Signatures , Effective Date, distribution list, reference guidelines, associated documents, objective, field of application, abbreviations, responsibilities

- **Identification**

SOP n°, version,

eg: Logistic – Regulatory – Monitoring ,..

SOP n° start with: 1 - 2 – 3 (eg: 101, 102,..) or L – R - S (eg: L01, ..)

- **Free text: SOP content**

SOP DOCUMENTATION SYSTEM

- **Writing, check, approval**

Specify language

Flow:

Written by : Field person –group possible

Checked by : Field person + skills in Quality and regulations

Approved by: Manager

Write an SOP: Synthetic,short sentences.

- **Who (at each step), what, when and how = FLow**
- Deadlines
- Pre-requisites
- Reference to working documents
- Updates process (If the SOP describes the issuing of a document)
- Where (filing)
- …

!! Consider risks: back-up, accident, recall , machine failure,

- **Training and Distribution**

Training before implementing the SOP: describe the process

Process for absent people

Electronic and hard copies. Acknowledgement of receipt

Training of new employees

- **SOP Update process**

Rhythm, initiation

- **Process for Derogation to a SOP**

Situations where applicable (exceptional)– request, approval and tracking

- **Versioning & archiving**

Versioning process,

Tracking of consecutive versions/revisions reason,

Filing of previous versions

Filing of applicable versions

Example of an SOP Format

Templates and Forms

- **Format and presentation**

Title & effective date

- **Fields and identification**

eg: Logistic – Regulatory – Monitoring – Quality

Identification: eg WDL, WDR,

WORKING DOCUMENTS SYSTEM

- **Writing, check, approval**

Specify language

Flow:

Written by : Field person –group possible

Checked by : Field person + skills in Quality and regulations

Approved by: Manager

Create a WD: synthetic,

Consider space for comments

- **Training and Distribution**

Training before implementing the WD: describe the process

Process for absent people

Electronic and hard copies. Acknowledgment of receipt

Training of new employees

- **WD Update process**

Rhythm, initiation – follows the related SOP

- **Process for Derogation to a WD**

Situations where applicable (exceptional)– request, approval and tracking

- **Versioning & archiving**

List of WD & effective dates

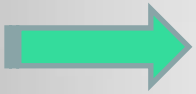
Filing of previous WD

Filing of applicable WD

Example of forms and template

HOW ARE YOUR SOPs and WORKING DOCUMENTS ISSUED & HANDLED ?

The process description



The SOP of the SOPs

SOPs in the field of QUALITY

Organization & functions of a Quality Unit

Documentation system

Quality Manual

Quality Control & Audit

Handling Derogation, Deviations, Change Control

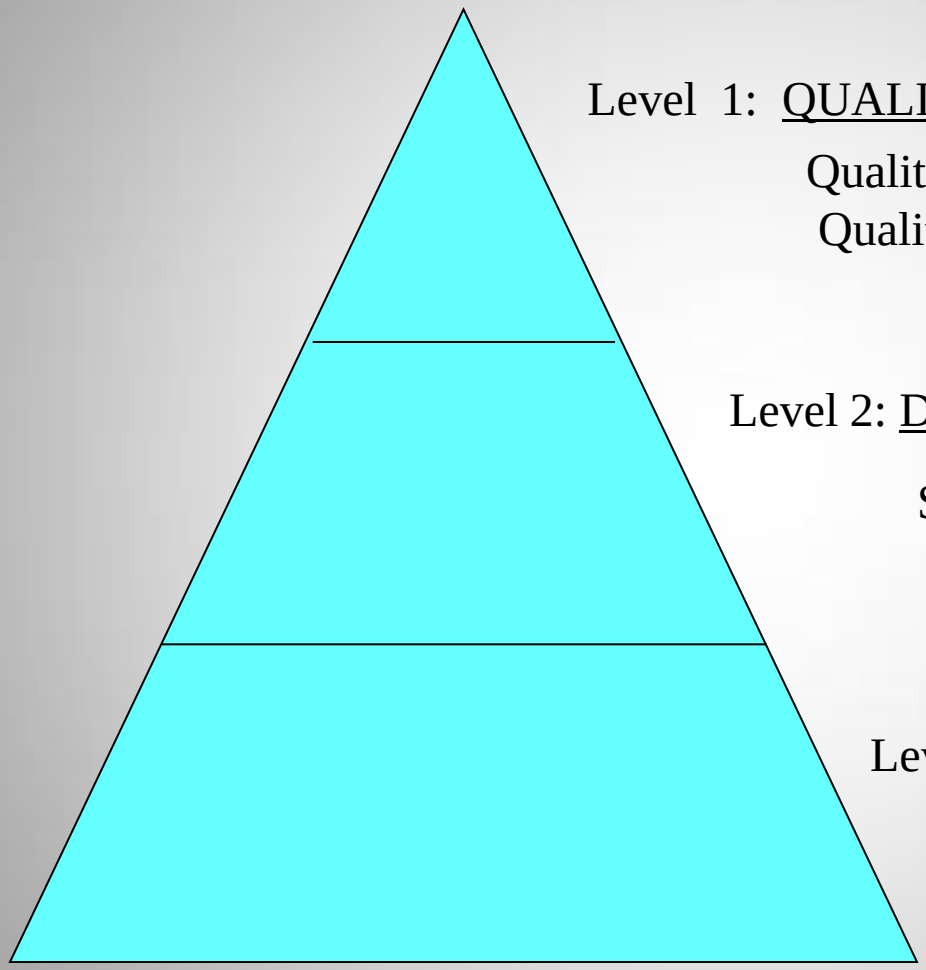
Handling CAPA

Training process

Indicators (performance, quality)

…

SAY HOW WE PERFORM



Level 1: QUALITY MANUAL

Quality Management System
Quality Documents Management

Level 2: Documents : SOPs

Standard Operating Procedures

Level 3: Working Documents

Forms - Templates

SPECIFIC TERMS

CHANGE CONTROL

DEROGATION

DEVIATION

CAPA

TMF

CHANGE CONTROL

Change control is a formal process used to ensure that changes to a product or system are introduced in a controlled and coordinated manner.

This standard process ensures that all planned changes are reviewed, assessed and approved by technical and quality-competent site personnel.

Steps in Change control

Request change

Justification (business or technical), feasibility, risk (impact on product quality and safety),

Plan

Test (transportation)

or

Implement gradually (test phase) (new process)

All steps should be documented/approved/..

Derogation

We derogate to a process, to a procedure (SOP)

Anticipated , planned beforehand

Request for a derogation should be formalized

(justified, submitted and approved by, a minima, a Quality function)

Deviation

Modification to a performance of an action supposed to be performed according to a SOP or a Protocol ..

Whether unexpected, or by force (no other alternatives)

= Unplanned modification

Should be always documented (explained), tracked, signed, by the person who performed the deviation

HOW TO DOCUMENT A DEVIATION

Write it down, explain reason why, write all efforts done to correct it, eg:

- **why the SOP/Protocol could not be followed**
- **why lab samples were not collected and shipped on time**
- **track telephone calls/mails**
- **describe new instruction, or correction implemented**
- **collect signature of appropriate persons (external, if applicable, and internal)**

and file the whole package

CAPA (Corrective Actions Preventive Action)

Takes place:

- **after an Audit, or an internal Quality control, ..**
  (Or when recurrent derogations or deviations occur)

- **usually in a table format**

It documents

- **the identified actions needed to correct or prevent the auditor observation,**
- **the responsible person,**
- **the deadlines,**
- **etc..**

Should be verified

- **by a field and a quality person**
- **in order to make sure and follow-up the corrective actions implementation**

THE TRIAL MASTER FILE (TMF)

Standard binders with standard sections, where all trial documentation is filed

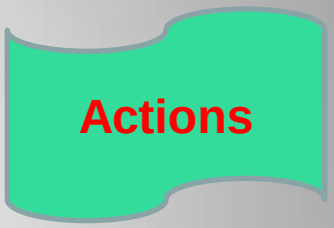
- **Regulatory section**
- **Trial documents section**
- **Trial IMP section**
- **Monitoring section**
- **Safety section**
- **Etc…**

- **Centres section (centre file)**

- **PERFORM AS WE SAID**
  - Apply the SOPS

- **DOCUMENT WHEN WE DID NOT/ARE NOT PERFORMING AS SAID**

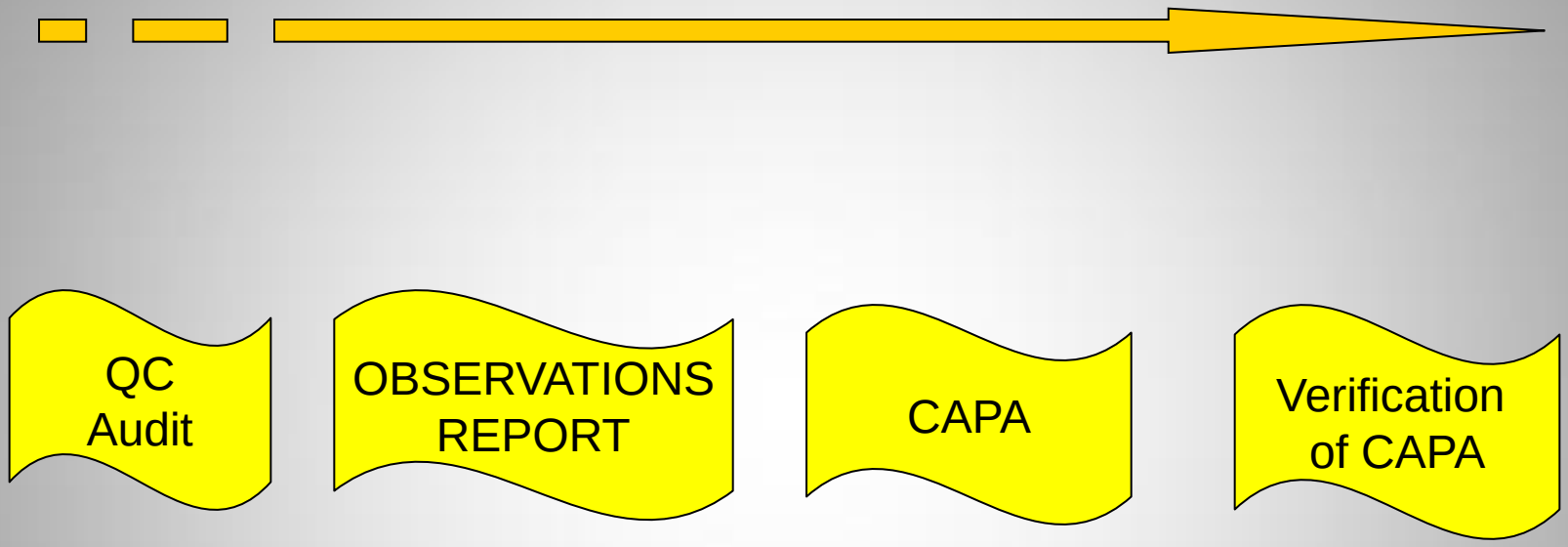
  - Derogations, Deviations, …..



  - Note to File …

AIM → **TRANSPARENCY**

CHECK THAT WE HAVE PERFORMED CORRECTLY



… BE IN CONSTANT PROGRESS…

Internal: QUALITY CONTROL

External: AUDIT

company cannot hire experts in all fields all the time

Auditors cover wider and are more expert than QC

Internal: QUALITY CONTROL

Verification of performance (actions, data collected, documentation, flow), compliance to SOP and to instructions

related to a field of work, or to a specific critical step, etc..

Example:

QC of a work flow: from receipt to return

All the files of a specific action: temperature management – monitoring

QC people are very familiar with the company internal process

External: AUDIT

KIND OF AUDITS

Site (investigator) Audit

Selection Audit of a subcontractor

System Audit

Audit for Cause

Site (investigator) Audit: most frequent

Audit of facilities, staff qualification, trial documentation,

Selection Audit: frequent : eg audit of a sub-contractor / CRO

Audit of organization, systems, SOPs, staff qualification, + technical issues ad hoc (eg: phase I facilities/equipments)

System Audit

Usually a company self audit: pharmacovigilance system audit or Biometry system audit

Audit for Cause

Usually at investigator site, sometimes at central labs, ..

INSPECTION (Authorities)

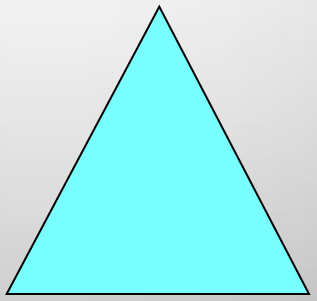
- **SAY HOW WE PERFORM**

INSPECTORS MAY REQUEST BEFOREHAND THE QUALITY MANUAL and/or DOCUMENTS, SOPs

QUALITY MANUAL

A Master document in which we describe the Quality Management System in our company

- **Organization**
- **Functions**
- **Tools**



THEN INSPECTORS SPEND 2 to 5 DAYS LOOKING AT IF WE

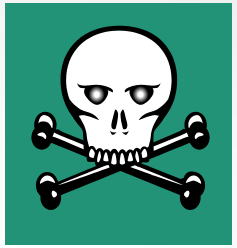
- PERFORM AS WE SAID

- DOCUMENT WHEN WE DID NOT PERFORM AS SAID

- CHECK THAT WE HAVE PERFORMED CORRECTLY

AUDIT or INSPECTION Outcome

Critical Observation



Major Observation

Minor Observation

A non critical deviation is tolerated

- As far as it has been documented, formalized (past & non recurrent deviation),

  IMP

- and that all effort has been taken and documented to avoid its recurrence (past & possible recurrent deviation)

  Patient diary

Some tips and suggestions

PREPARE BEFORE AN AUDIT or INSPECTION (1/5)

- Mobilized and available staff
- Prepare documentation
- Identify locations and contact persons
- Designate audit interlocutors → interviews
- Prepare a quiet meeting room

- Prepare a « back-office » room (inspection) – on line requests – briefing before and after

During the audit/inspection (2/5)

Oral explanations are never sufficient

You will be asked to:

- « yes , we have been trained »

- ***Show SOP on training***
- ***Show record of the training sessions***
- ***Show HR/Quality dept SOP***

- « no, nobody goes in if not wearing a badge,… or if not registered»

- ***Door keeper presence time***
- ***Entries registry***
- ***Badge machine (valid ? Checked ?)***
- ***Related SOP***

During the audit/inspection

(3/5)

Don’t forget essential behaviors

- ***Lock the archiving room door***
- ***Ware the protection suit***

During the audit/inspection

(4/5)

BE PREPARED FOR QUESTIONS ON BACK-UP AND RISKS

GIVE ANSWER ONLY TO THE QUESTION – AVOID:

- *"For the remaining…forms…*
- *"As far as …the IP has not expired…*
- *"Unless the trial…is double blind…*

BE PROFESSIONNAL AND ONLY NICE (oriental Vs occidental culture)

During the audit/inspection

(5/5)

REMAIN TRANSPARENT AND HUMBLE

- **Being in a progress process is a RIGHT**
- **Pretend everything is Okay is a big CLUMSINESS**

GCP

quality standard

that the data are credible

and the rights, safety, integrity and confidentiality of the subjects are protected

HOW ???

KEEP IN MIND

QUALITY IS:

- SAY HOW WE PERFORM
- PERFORM AS WE SAID
- DOCUMENT WHEN WE DID NOT/ARE NOT PERFORMING AS SAID
- CHECK THAT WE HAVE PERFORMED CORRECTLY