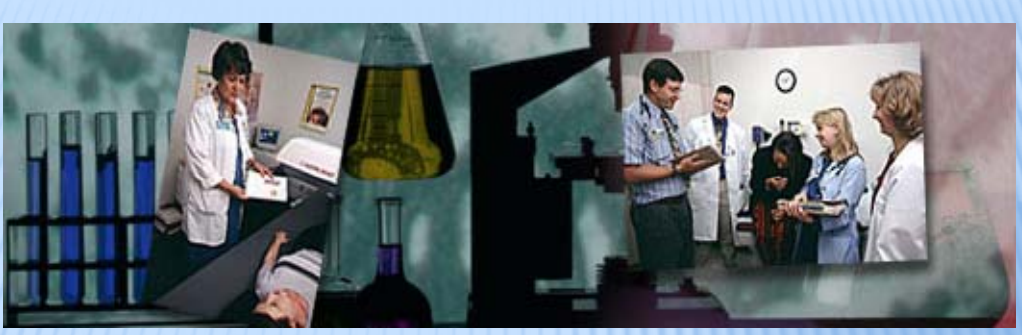
GCP:
Responsibilities of the Monitor

Monitoring Plan
Monitoring Report

Agenda

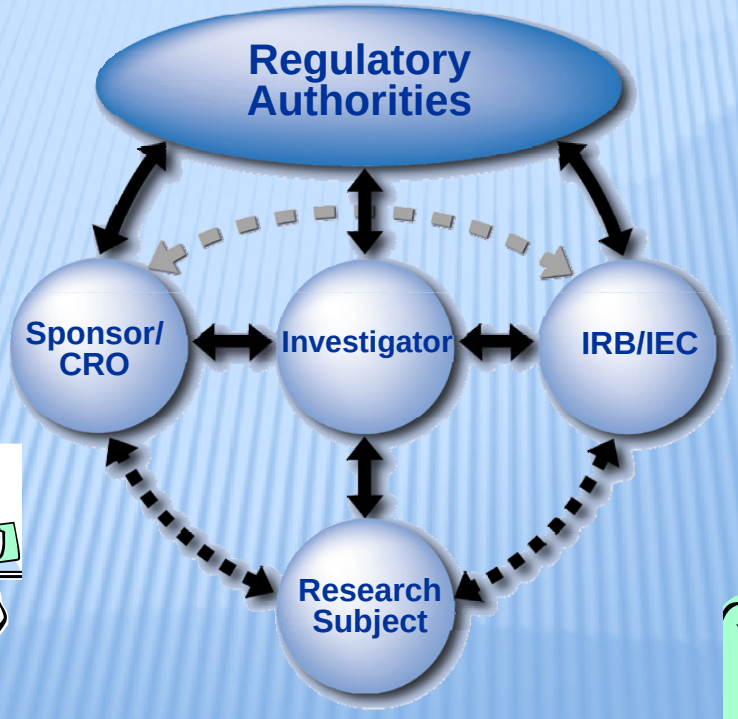
- **Why monitoring is necessary**
- **Which are the duties of the clinical monitor and how are accomplished**
- **Which are the documents produced by the clinical monitor**

Monitoring is mandatory according to Good Clinical Practice



GCP defines a sequence of actions to be done in every clinical study in different workplaces far away each other.

Logical schema of GCP



Outsourcing = CRO

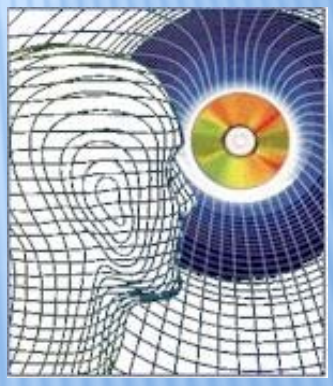
Pharmaceutical Companies design and plan internally clinical studies, but …….

….. delegate the whole operational implementation to 3rd parties (Contract Research Organisations)

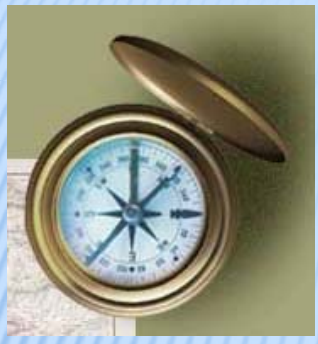
CLINICAL MONITOR or CRA (clinical research associate)

This is the person delegated by the Sponsor to select suitable investigational sites and to follow and verify the correct study implementation at the selected sites.

This person must be trained both to the sense and the practice of monitoring and to the protocol and all other study specific documents.



Which are the documents to be followed by the CLINICAL MONITOR?



- **ICH GCP**
- **other national laws about clinical studies**
- **the SOPs**
- **the protocol and its attachments**
- **possible study-specific manuals**

DUTIES of the CLINICAL MONITOR

Verifies that:

informed consent, admission criteria, etc.

- **Rights and wellbeing of subjects are protected**
- **The study data, either paper or electronic, are accurate, complete and traceable by means of source documents**
- **The study conduct is absolutely compliant to the approved protocol, to ICH GCP, to other applicable regulations and to standard operating procedures being a reference for the study**

VISITS at SITES

The kinds of visits may be the following:

ASSESSMENT

PRE-STUDY

INITIATION

MONITORING

TERMINATION

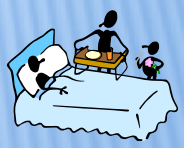
Interactions of the monitor

other departments

investigator

pharmacist

CRA



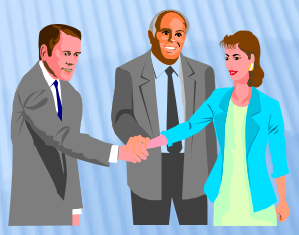
co-investigators

Ethics Committee

administration

PRE-STUDY VISIT

AIM:



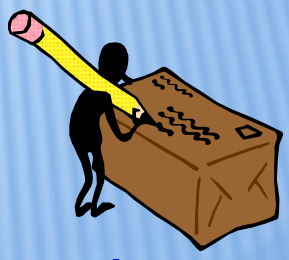
- **Identify the investigator**
- **Evaluate the site staff for the study is qualified and adequate**
- **Verify that the structure and instrumentations are adequate**
- **Verify the availability of the required number of patients**

INITIATION VISIT

AIM:

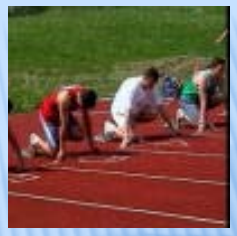
- **to discuss all protocol procedures with all site staff before the study start including the informed consent**

  It is made only after all required approvals and the receipt of all study materials by the site:



- ✓ **CRFs**
- ✓ **Laboratory materials**
- ✓ **Investigational drug(s)**
- ✓ **Investigator's file**
- ✓ **Randomization procedures or envelopes**

INITIATION VISIT



Topics to be discussed in details:

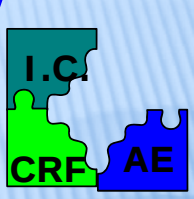
- **schema of the treatments and drug accountability**
- **laboratory procedures**
- **admission / exclusion criteria**
- **procedures to notify adverse events**
- **forms to be filled in by the investigator**

The report of this visit must be filed at investigational site too

What is verified by the monitor during routine monitoring visits to sites

- CRF vs source documents
- Site organisation (staff/CV s, instruments/calibration/maintenance, training)
- Regulatory documents
- Investigational drug(s) (custody and accountability)
- Informed consents (signatures and versions)

MONITORING VISIT



All the following is controlled:

- **signed informed consents,**
- **compliance to the protocol and subjects eligibility, source documents against CRF**
- **enrollment and randomization**
- **drug accountability and Investigator's File**
- **AE / SAE**

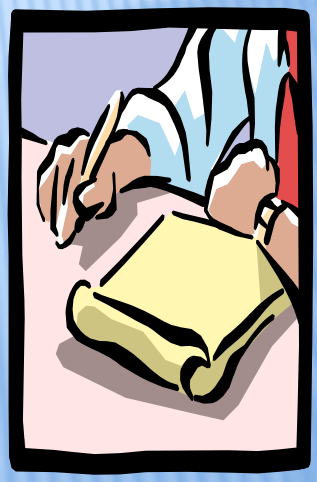
A few words about DRUG ACCOUNTABIITY ....

- **It's a boring operation: both investigator and monitor don't like it**
- **May be an explanation of AE for overdose or incorrect doses**
- **It's a duty of the investigator to record it and of the monitor to control it**
- **It is an important step: it's the confirmation that the study result can be linked to the right dose(s)**

MONITORING VISIT

MONITORING VISIT REPORT

- **The Clinical Monitor must prepare a written report about the visit**
- **This report must include the description of all performed controls, discussed topics, compliance deviations, weakness points, possible agreed corrective actions or given suggestions to guarantee the respect of the protocol and GCP**
- **The REPORT of the visit is to be filed in the TRIAL MASTER FILE at the SPONSOR .**



MONITORING VISIT FOLLOW UP

FOLLOW UP LETTER to the INVESTIGATOR

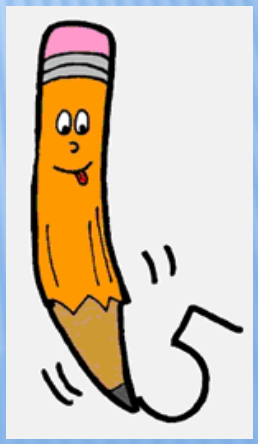
The description of:

- **discussed topics,**
- **compliance deviations,**
- **weakness points,**
- **possible agreed corrective actions or given suggestions**

is made in a letter or e-mail to the principal investigator in order to assure the correction of the wrong aspects of the site and to prepare following monitoring visit

Documents produced by the monitor

- a specific report for each monitoring visit
- follow up letters to the investigator
- list of GCP and/or protocol violations/ deviations of the investigational site



Tools for the monitor

Source data agreement

- how are available source data
- where are kept
- when are available

TERMINATION VISIT

Main activities:

- **to discuss the archiving of study documents**
- **to remind the investigator his responsibilities and the possibility of future inspections or audits**
- **to verify the completeness of the Investigator's File before archiving**
- **to verify the return of used/unused investigational drug(s)**

From Good Clinical Practice Guide published by MHRA (Medicines and Healthcare products Regulatory Agency, UK) in 2012

It is the responsibility of the sponsor to ensure that trials are adequately monitored. Therefore, the sponsor must determine the appropriate extent and nature of monitoring; this should be based on the objective, purpose, design, complexity, size, blinding and end-points of the trial as well as the risk posed by the investigational medicinal product and trial-related activities, and the experience of the investigator sites. It is recommended that this is identified via the trial risk assessment and clearly documented (for example, in the form of a monitoring plan).

Content of the Monitoring Plan

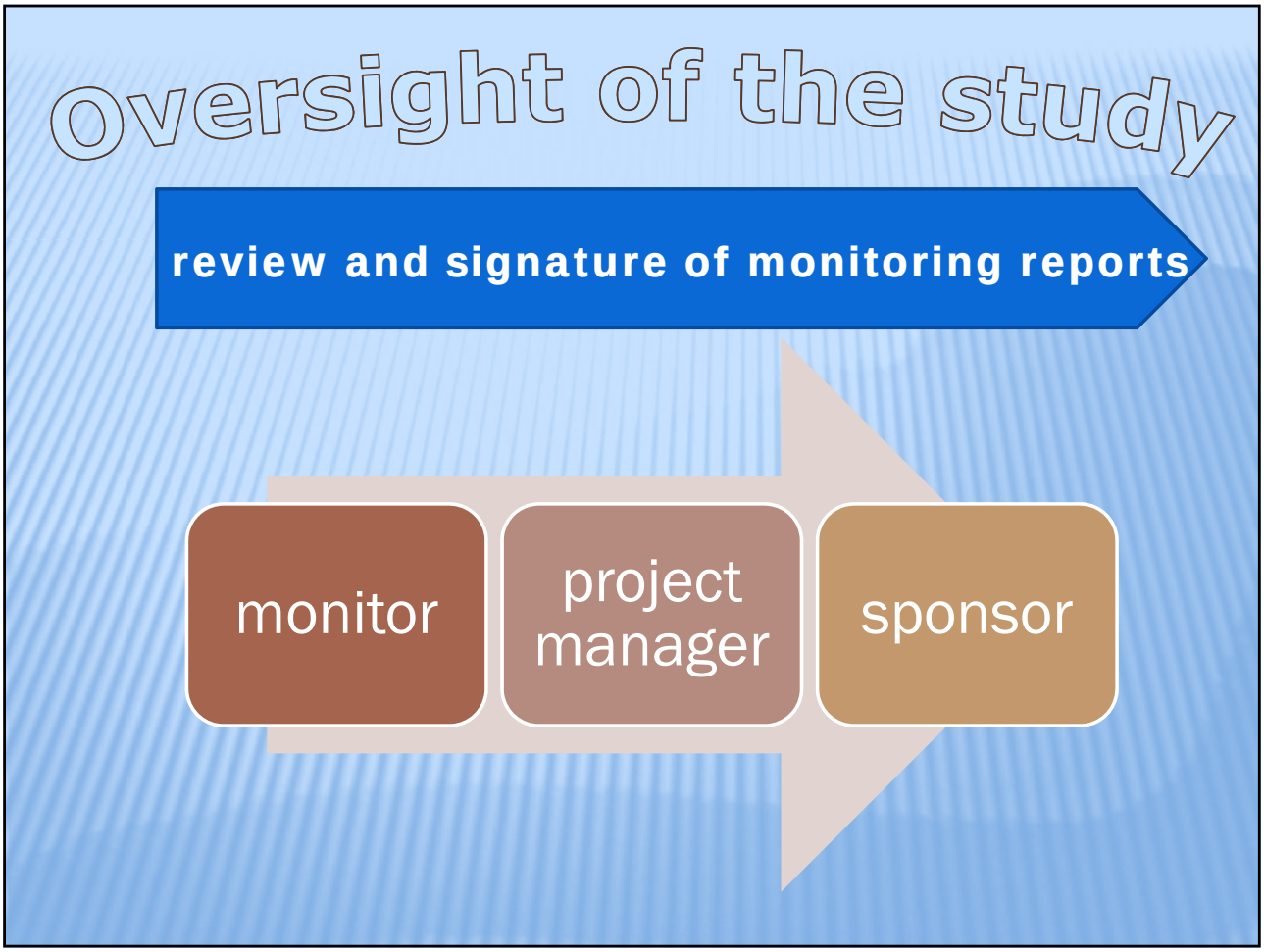
- study population, eligibility criteria
- frequency of monitoring visits, number of sites and of monitors
- data to be reviewed (percentage of SDV required and on what data)
- ancillary departments to be visited (such as pharmacy, laboratories, imaging, etc.)
- SAE reporting and associated monitoring responsibilities
- how non-compliances will be recorded and circulated
- escalation of actions
- query management

... all this must be described with a real reference to the study and not with standard and generic phrases that are absolutely identical for whichever study !!

"ad hoc" reference documents

Monitoring Plan

- study-specific
- List of data and information to be entered by the investigator in the Hospital Chart of the patient
- List of examination reports to be filed by the investigator together with the Hospital chart
- An useful tool would be to have a copy of each page of the CRF annotated with all aspects to be considered for each single section


Oversight of the study
review and signature of monitoring reports
monitor
project manager
sponsor

The chain of custody of the data

The monitor is the first control of its robustness

Chain of custody of DATA

1. Clinical charts, examinations results, images, etc.

2. CRF filled in accurately

3. Data management & analysis

The data transfer must be traced in both directions (one way/ return) and no one of the actors must be the only one to have them.

What is needed:

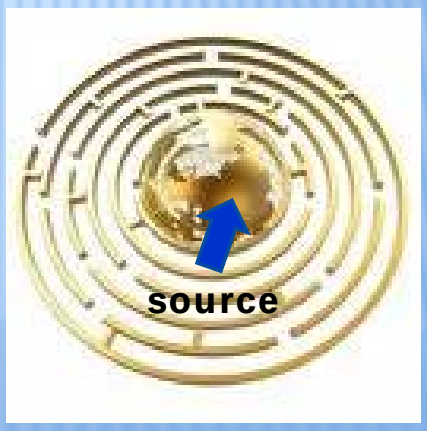
- **attention to details of the protocol how it is written**
- **GCP knowledge and what it is meant translated into the specific study**
- **attitude to register carefully and on time the results together with relevant environmental conditions at site**

In one single word ….

TRACEABILITY

Chain of custody of DATA

During its journey, original data don't move. Only its copy or transcription goes to the next step (source data concept).



E Source

It is possible that the result of an examination is e electronic, i.e. a “virtual data”. In this case the computerized system producing it:

1. Must be validated (i.e. reliable for the intended purpose)
2. The datum itself must stay with the site, that means that can not be downloaded into the server of the sponsor, because it pertains the subject and the hospital: only one copy may be transferred

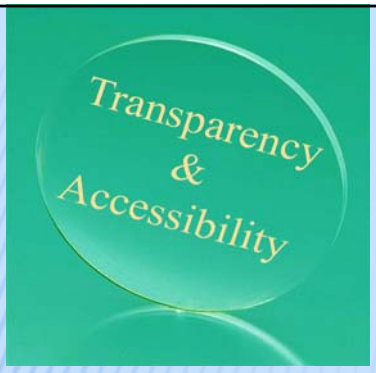
The location of source documents and the associated source data should be clearly identified at all points within the capture process. (Requirement 11, ICH GCP 6.4.9)

……..

The source data and their respective capture methods should be clearly defined prior to trial recruitment (i.e. in the protocol or study specific source data agreement). The sponsor should describe which data will be transferred, the origin and destination of the data, the parties with access to the transferred data, the timing of the transfer and any actions that may be triggered by real-time review of those data.

There should only be one source defined at any time for any data element.

Reflection paper on expectations for electronic source data and data transcribed to electronic source collection tools in clinical trial
EMA 09 June 2010 § 6.2 topic 2 page 9/13



The Computer Validation must respect the GCP to generate a correct eSource

The regulatory guidelines underscore that the computerized system must be accessible in every time to those having the right to see it, that means:

1. the patient must have access to her/his examination result, diary, etc.
2. The investigator, who is his doctor, must have the same access at every time

Never the sponsor must have the “exclusive and absolute control” of the data

Source data verification

In the practice the monitor answers the following questions:

The data:

Are for sure of the patient?

Have been registered by the investigator ?

Have been captured when created or are the result of recollections and remembering?

Will remain legible in the future?

Reference documents:

Reflection paper on expectations for electronic source data and data transcribed to electronic source collection tools in clinical trial

EMA 09 June 2010

Coming into effect on 01 August 2010


Thank
You!