Quality Management Systems

GCP/ICH & Inspections

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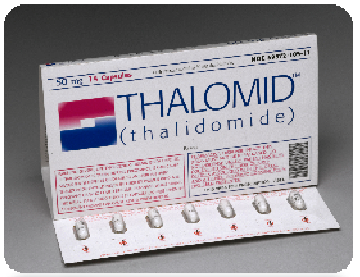
June 2nd 2016
Rio de Janeiro - Brazil

Where did GCP come from?

Unsafe Medicines / Poor Testing
Thalidomide Disaster
(Babies were born with malformation of the limbs)



Human Rights Abuses *
War Crimes
Prison Populations
Mentally Ill

Poor Quality / Fraudulent Data
Fictitious Patients

GCP

***The Tuskegee Syphilis Experiment**

What is GCP?

Safety of subjects

Standard of data

The Aim of GCP

GCP ensures that:

- ❖ Subjects are properly protected in studies.
- ❖ Studies are based on good science, are well designed and properly analyzed.
- ❖ Study procedures are properly performed and documented.

If GCP not followed:

- ❖ Participating subjects may be at risk.
- ❖ Data collected may be unreliable.
- ❖ Study will be rejected by Boards of Health.

Historical Overview

1947	Nuremberg Code
1963	IND procedures (USA)
1964	Declaration of Helsinki (18th World Medical Assembly)
1968	Medicines Act (UK)
1978	FDA GCP Guidelines (USA)
1983	WHO Declaration of Helsinki endorsement
1987	Bonnes Pratiques Cliniques (French law)
1989	Nordic GCP guidelines
1991	CPMP Directive (EC-directive)
1992	Australian guidelines = WHO draft guidelines
1993	WHO Guidelines
1996	ICH GCP Guidelines

Helsinki Declaration

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Developed by the "World Medical Association".

Objective

- **Ethical principles guiding physicians and the WMA encourages others who are involved in medical research involving human subjects to adopt these principles.**

(Adopted in Helsinki, Finland June 1964).

"The health of my patient will be my first consideration."

"A physician shall act in the patient's best interest when providing medical care."

http://www.wma.net/en/30publications/10policies/b3/

Helsinki Declaration: Principles

- **Scientific Requirements and Research Protocols:** design described & justified, statement ethical principles.
- **Evaluation of benefits/risks:**
  Objectives in proportion to risks, more good than harm, interests of subject prevail, stop if risks outweigh benefits.
- **Vulnerable Groups and Individuals**
- **Research Ethics Committees**
- **Privacy and Confidentiality**
- **Subject Informed Consent**
- **Post-Trial Provisions**
- **Research Registration, Publication and Dissemination of Results**
- **Qualifications of researchers:**
  Scientifically qualified staff, medical supervision, end responsibility rests with medically qualified persons.
- **Unproven Interventions in Clinical Practice**
- **Use of Placebo**

http://www.wma.net/en/30publications/10policies/b3/

Subject Informed Consent

Prior to the beginning of the trial: PI should have written favorable Regulatory approvals.

- **Subject voluntary / capable confirms willingness to participate.**

  - Incapable subject, physician must obtain IC from legally authorized representative (witness if applicable).

- **Subject must be informed of all aspects of study** (minors, or patients with severe dementia).

- **Process should be documented in source documents / medical records.**

- **Give subject enough time to ask questions witness answered subject´s satisfaction.**

Subject Informed Consent

- **New Info Available:**

"Whenever important new info available (Amendments) that may be relevant to the subject's consent, the same approval process should be done and the subject should decide whether continuing in the study."

- **Non-Technical Language:** oral and written information.

- **Consent should be given in written, signed, dated:**

"Prior to a subject's participation in the trial, the written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion."

Subject Informed Consent

•If a **subject is unable to read** or if a legally acceptable representative is unable to read, “an impartial witness” should be present during the entire informed consent discussion.

“All parties have to sign the ICF after explanation!”

• **A copy of the ICF must be given to the subject after its signature (≠ Countries).**

• **Emergency situations:**

o Subject can be included in the study only if previous consent (Subject/LR) is not possible. Enrolment in accordance to protocol and favorable IRB/IEC approval received.

o The subject or LR should be informed about the trial as soon as possible and consent to continue should be requested.

Clinical Trial: Potential Benefits

- Access to promising new treatments (no cost) often not available outside the clinical-trial setting.

- **Treatment that may be more effective than the standard approach** (Close monitoring, advice, care, and support by a research team of doctors (experts) who understand your disease or condition).

- The opportunity to be the **first to benefit from a new method** under study.

- The chance to play an active role in your own healthcare and gain a greater **understanding of your disease or condition**.

- **Help society by contributing to medical research**. Even if you don't directly benefit from the results, the information can help others and adds to scientific knowledge (improving medical care).

- **PIs play an important role in the development of products to combat disease**, treat chronic and degenerative diseases, and improve the health of people around the world.

ICH International Conference on Harmonisation
Guideline for Good Clinical Practice

“MISSION”

Make recommendations to reach harmonisation in the guidelines / requirements for product registration, reducing / avoiding duplication of testing during trial and development of New Human Medicines.

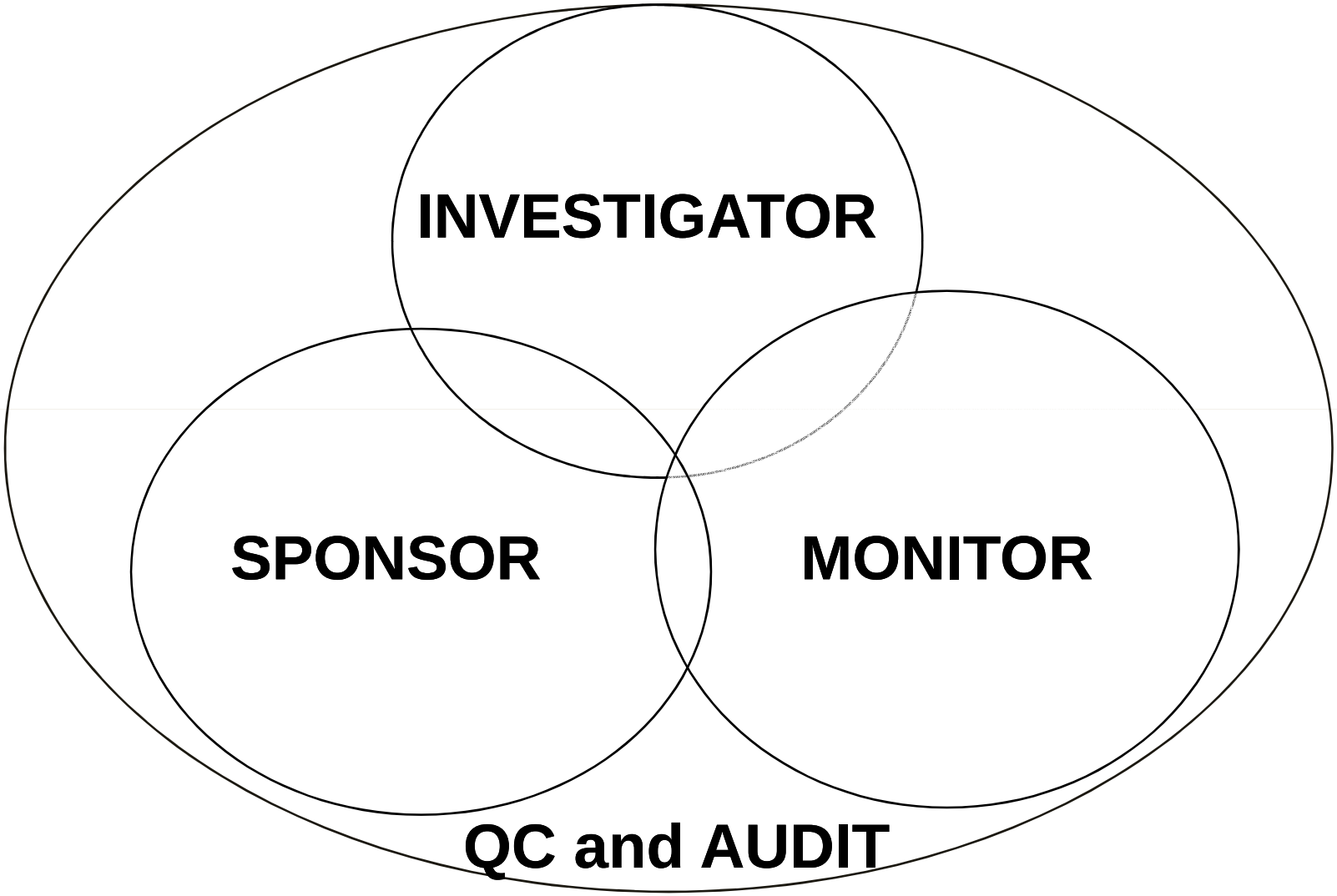
ICH (Efficacy Guidelines - E6*):
International ethical and scientific quality standards
FOR: Clinical Trial design, management, oversight, conduct, documentation /recording and reporting …
THAT: will better ensure human subject protection and data quality.

*Guideline for good clinical practice E6 (R2) under revision. End of consultation, deadline for comments Feb 03 2016

ICH: Steering Committee

http://www.ich.org/about/organisation-of-ich/steering.html

Key Roles & Responsibilities



Sponsor (ICH 1.53)

Individual, company, institution, or organization, responsible for the initiation, management, and/or financing of a CT.

RESPONSIBILITIES:

- Write protocol detailing all the procedures necessary to conduct the trail.
- Develop clear **processes and procedures (SOPs),** detailing how the sponsor will manage the trial, handle the data and keep records.
- Submit application and obtain approval from regulatory authorities before the start of the trial.
- Safety:
    - Ensure **ongoing safety evaluation** of the product.
    - **Notify** all concerned of **any issue with the product,** expedite Adverse Drug Reaction Reports as per regulations.
    - Keep **updates of safety** maintained to relevant **authorities.**

Sponsor Responsibilities ?

(ICH 1.53)

- **Monitoring:**
  - Have clear monitoring processes and procedures detailing how the sponsor will manage the Site.
  - Ensure that GCP requirements, company protocol and SOP requirements are being adhered to.
- **Medical expertise & qualified personnel (CRO).**
- **Investigational Product : information , manufacturing, packaging, labelling, coding, supplying.**
- **Implement and Maintain Quality Assurance & Quality Control.**
- **Study reporting.**
- **Investigator / Site Selection.**

Who is the Investigator?

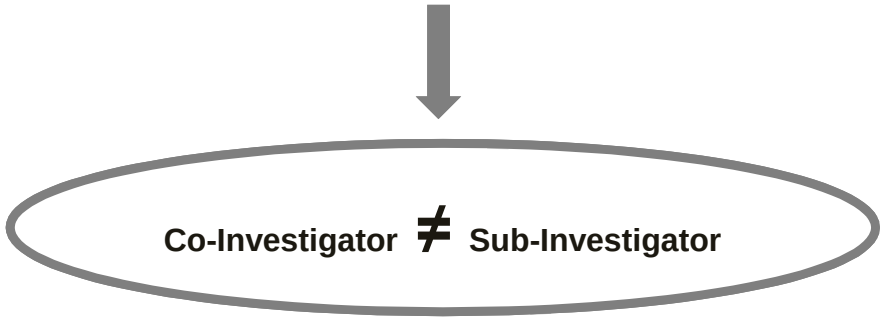
The Investigator (ICH 1.34):

"A person responsible for the conduct of the clinical trial at a trial site.

PI is the responsible leader of the team and may be called the PI".

The Co-Investigator (ICH 1.56):

"Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial related procedures and /or to make important trial related decisions (associates, residents, research fellows).



Investigator Responsibilities (ICH 4.1-13)

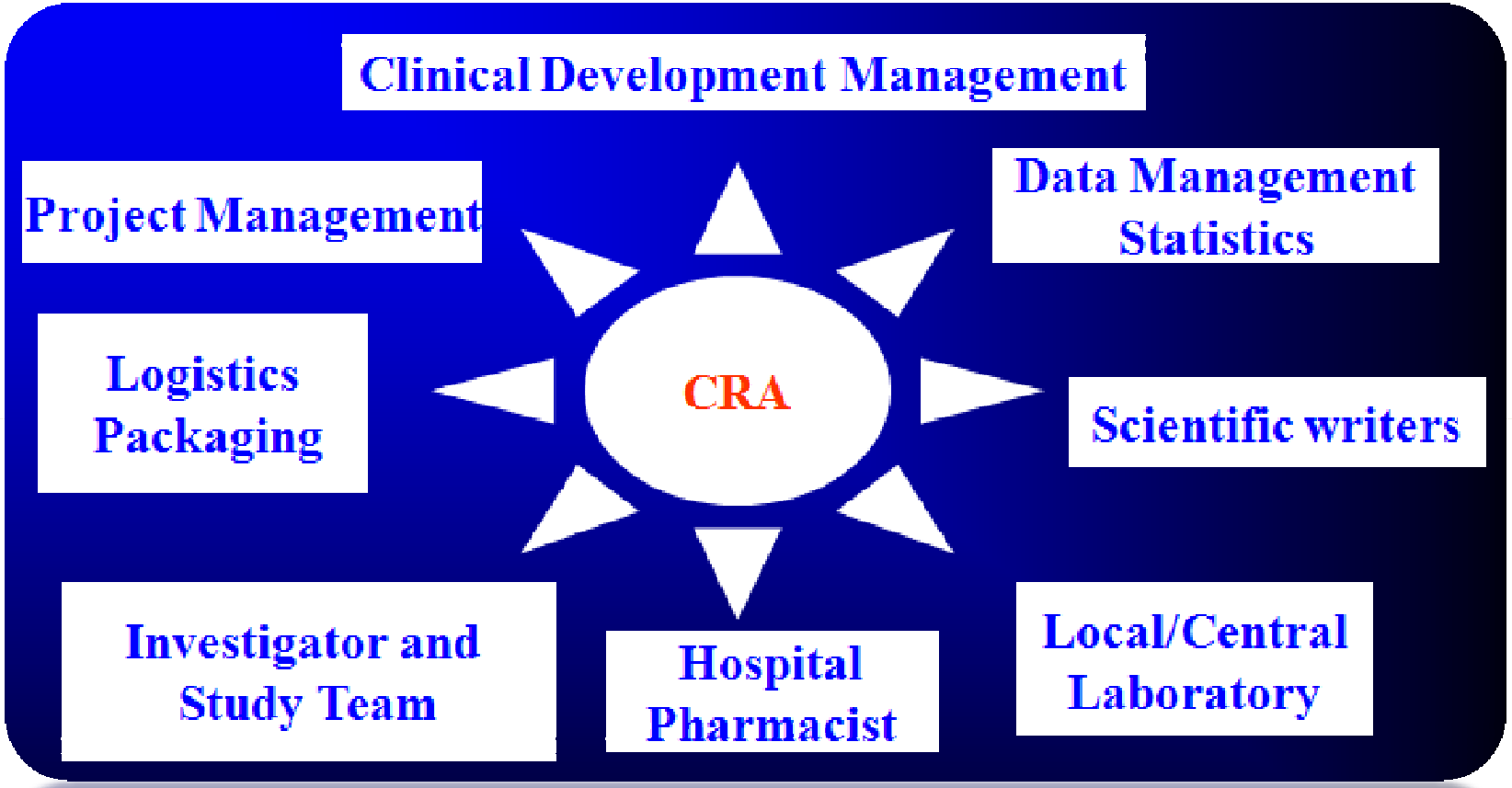
Agree and comply to the last version of Protocol/ Study Documents.	<u>Investigational Product :</u> Accountability & Cold Chain maintenance.
Regulatory responsibilities: Obtain IEC/IRB approvals and maintains constant communication.	Safety: AE/ SAE Reporting and follow up.
Staff Qualification / Training / Meetings / Delegation of Responsibilities.	Meetings Participation / Communication: Sponsor representatives (Auditors) / Regulatory Authority (Inspector) and others.
Subject Selection & ICF.	Records, Documents, Data archiving.
Ensure the protection of the subject's right, safety and welfare.	Agreements.
Medical care of trial subjects.	Adequate study site.

Monitor Responsibilities

Appointed by the sponsor to monitor the trial, ensures that:

- Data and reported results are complete, credible and accurate and that the rights, integrity and confidentiality of trial subjects are protected.
- Conduct of the trial is in compliance with the currently approved protocol /amend.(s), GCP and Regulatory Requirement(s).
- Main line of communication between the Investigator and Sponsor.
- Promotes good study conduct by supporting site staff.
- Submit written reports after the visit, relevant phone call, letter or other contact with investigator.

Central Position of Monitor



Review of Keys to a Successful ICH/GCP Trial Sponsor / PI

- Follow ethical principles.

- Outweigh: foreseeable risks, anticipated benefits.
- Ensure timely and efficient safety reporting.
- Have adequate non clinical and clinical information to support the trial.
- Write a clear and detailed protocol that is scientifically sound.
- Obtain favorable IEC/Regulatory opinion.
- Follow the protocol meticulously.

Rights, safety and well-being of trial subjects prevail over interests of science and society.

Review of Keys to a Successful ICH/GCP Trial Sponsor / PI

- Ensure the study team members are correctly qualified, trained and experienced.

  → Medical care: qualified physician.

- Obtain freely given ICF.

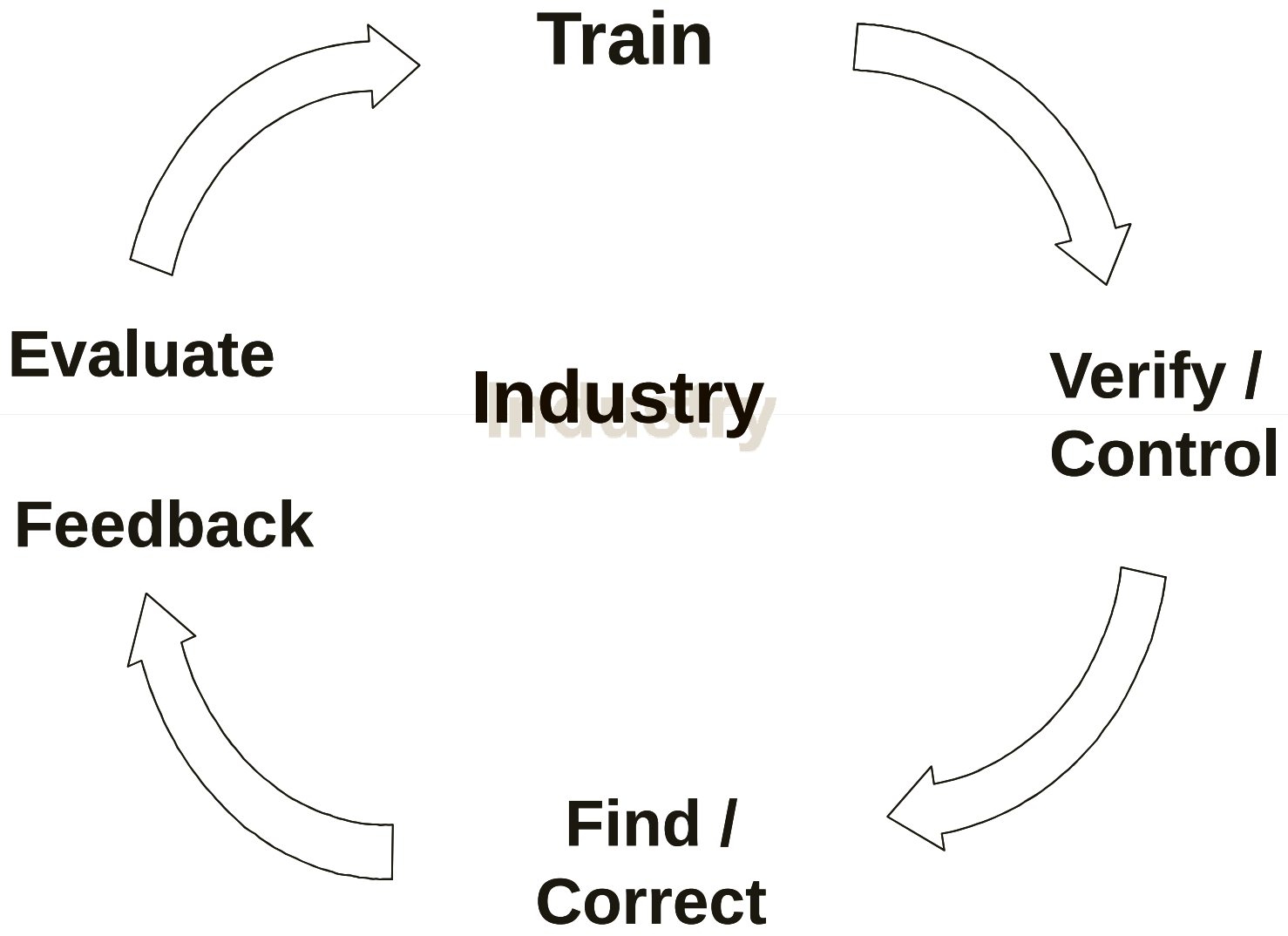
- Maintain good study files.

- Respect confidentiality and privacy rules.

- Vaccines: Respect GMP and protocol.

- Safeguard the quality at all time. → Monitoring Process

Site will be prepared for AUDIT & INSPECTION



What is FDA's role in approving New Drugs and Medical Treatments?

FDA makes sure medical treatments are safe and effective for people to use.

FDA staff meet with researchers and perform inspections of clinical trial study sites

to protect the rights of patients

and to

verify the quality and integrity of the data.

FDA - The Investigational New Drug Process

Drug developers, or sponsors, must submit an Investigational New Drug (IND) application to FDA before beginning clinical research.

<u>In the IND application, developers must include:</u>

- **Animal study data and toxicity (side effects that cause great harm) data.**
- **Manufacturing information.**
- **Clinical protocols (study plans) for studies to be conducted.**
- **Data from any prior human research.**
- **Information about the investigator.**

FDA Approval

FDA Team has 30 days to review the original IND submission.

The process protects volunteers who participate in clinical trials from unreasonable and significant risk in clinical trials.

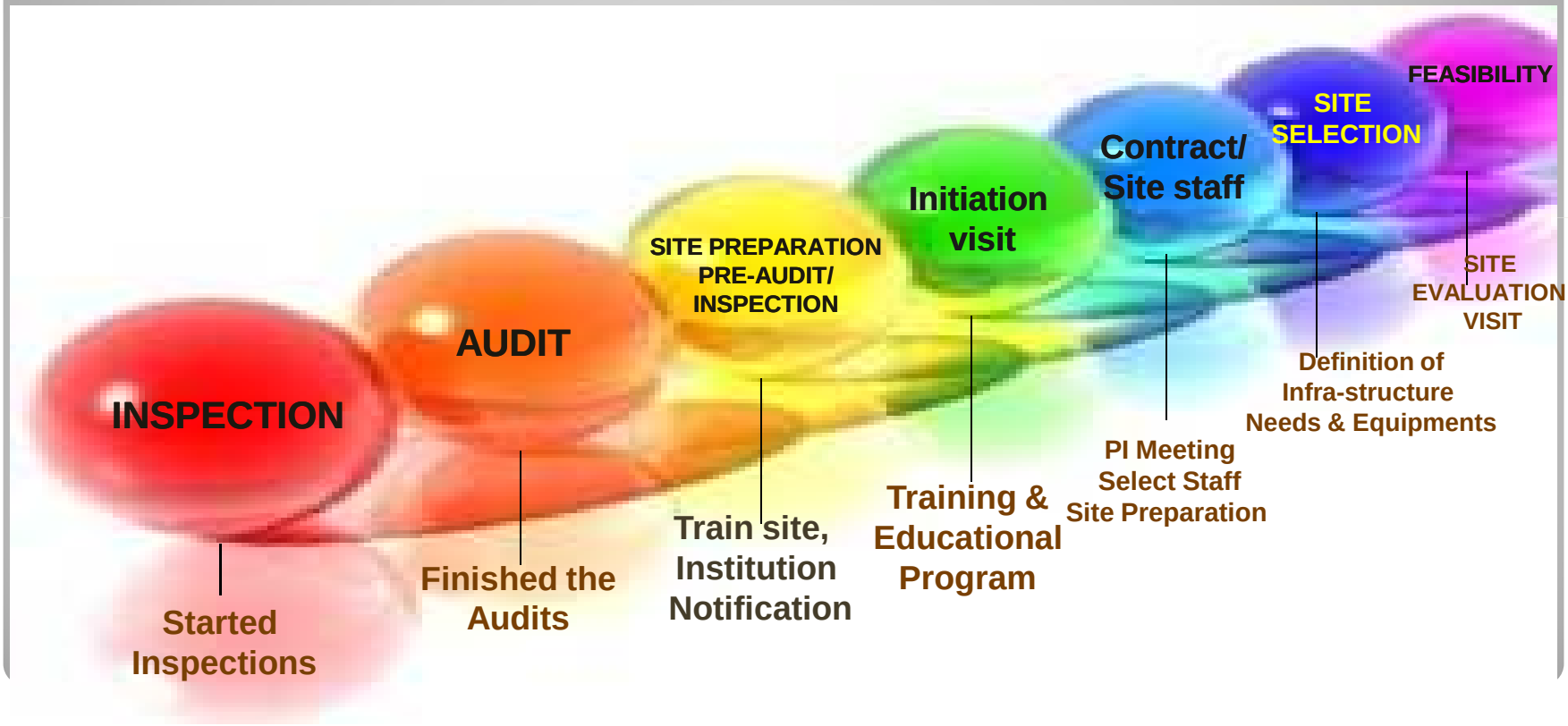
FDA responds to IND applications in one of two ways:

- **Approval to begin clinical trials.**

PI / Staff
FDA 1572 Form
Financial Disclosure

- **Clinical hold to delay or stop the investigation. FDA can place a clinical hold for specific reasons, including:**
  - Participants are exposed to unreasonable or **significant risk.**
  - **Investigators** are **not qualified.**
  - **Materials for the volunteer are giving the wrong idea or impression.**
  - The IND application does **not include enough information about the trial's risks.**

CLINICAL TRIALS:
Audits & Inspections



How to Prepare a Site for AUDIT or INSPECTION?

Key Difference: Inspection x Audit

Inspections

1 **Performed by regulatory agencies**

- **Food and Drug Administration**
  http://www.fda.gov
- **Ministry of Health for each country**
- **European Medicine Agency – EMA**
  http://www.ema.europa.eu

Audits

2 **Performed by the industry**

Other Differences

Audits

- In audits, the professionals are employed of the company who work for an active clinical quality assurance function (Industry / CRO).

- The aim of the audit is ensure that a site is complying with the protocol, SOP, GCP/ICH and the applicable regulatory requirements.

Inspections

- During inspection the inspectors are employed by government through the agency of the regulatory or competent authority (FDA, MOH…).

- The goal is to ensure that the trial related obligations and the acceptability of resultant clinical data is in support of a new drug approval.

Audit Definition

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.

" *Section 1.6 of the 'International Conference on Harmonisation Guideline on Good Clinical Practice' ('ICH-GCP')*

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Ref_www.ich.org

Audit Objective

Informal and Planned Process

The exchange of information between the Auditor and Site Staff is acceptable and is mainly used as an evaluation tool.

Results should be used to train staff and improve upon the quality of research conducted. Very often an internal audit is undertaken prior to an external inspection.

TO OBTAIN GOOD RESULTS !

*Ref.*4_Guidelines on Preparing for Audit and Inspection in Clinical Research, Milton Keynes Hospital NHS Foundation Trust, Feb,02,2010*

Inspection Definition

"An act by a Regulatory Authority of conducting an official review of documents, facilities, records and any other resources that are judged by the authority to be related to the clinical trial and that maybe located at the site of the trial, at the Sponsor and/or CRO's facilities or at other establishments judge appropriate by the Regulatory Authority"

Section 1.29 of the 'International Conference on Harmonisation Guideline on Good Clinical Practice' ('ICH-GCP')

Ref_www.ich.org

INSPECTION Objective

An inspection is a “formal’ process that has legal implications if non-compliance with the regulations is found.

Is very often “notified” unless the Authority has concerns for patient safety or grounds to suspect that improper practices are occurring at a site.

Inspectors have the legal right of entry to inspect premises at any time without notification.

It is therefore essential that all trial related documentation is maintained and continually updated in readiness for an inspection ! !

*Ref.*5_Guidelines on Preparing for Audit and Inspection in Clinical Research, Milton Keynes Hospital NHS Foundation Trust, Feb,02,2010*

INSPECTION Summary

- **Verify data**

- Quality & Integrity

- **Ensure subject protection**

- Rights, safety & Welfare Quality & Integrity

- **Verify complience**

- Protocol and study documents

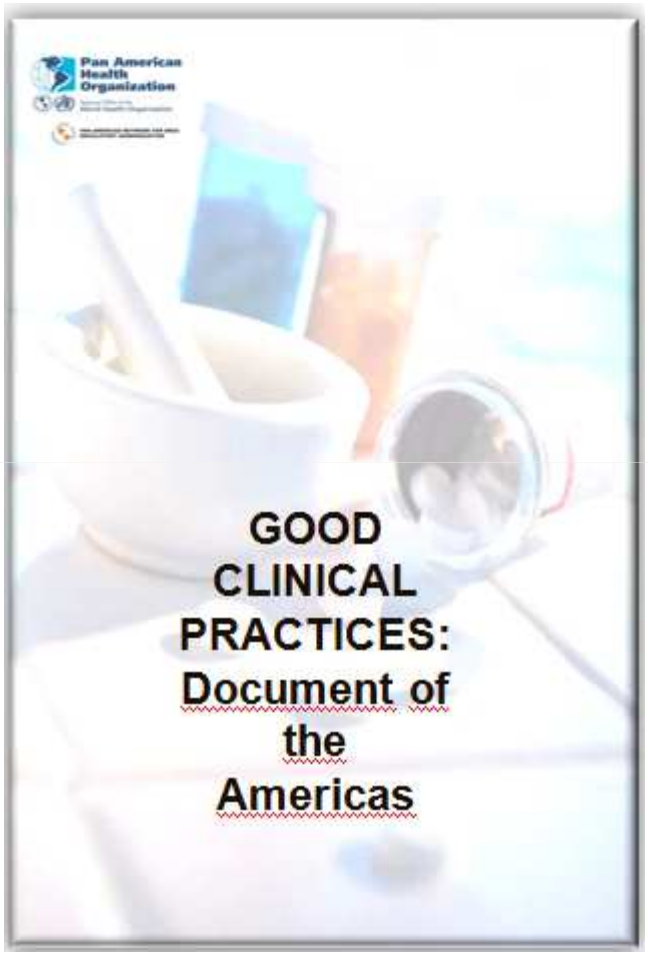
- **Verify the control of study medications**

- **Decision making**

- Safety & Efficacy

- **Facilities Evaluation**

INSPECTION: “Document of Americas”



Planning the inspection / Selection of the studies

Inspections can be conducted before, during or after a study is completed.
Considering that it is not possible to inspect all studies in a country, the 1st step in the inspection process is to decide which studies are to be inspected.
Each country should establish written criteria for selecting studies to be inspected.

<u>This criteria may include:</u>

Importance of the trial for regulatory decision-making;
Nature of the study;
Vulnerability of subjects;
Data irregularities;
Complaints

Document of the Americas was officially adopted by the IV Pan American Conference on Drug regulatory Harmonization on March 2005.

Audits & Inspections: Key Differences Among

Industry

1

Garantee

- **The data quality.**
- **Protocol activities were respected.**
- **Regulatory documentation.**
- **The sponsor SOP, GCP/ICH and the applicable regulatory requirements were followed.**
- **The sponsor has primary responsibility for monitoring the study etc.**

National Regulatory

2

Primarily intended verify:

PI/Staff, Study Sites, Safety, Essential Docs, Drugs, Labs Procedures, AEs/SAEs, ICF, Facilities and Equipments available to support the trail.

They can inspect the institution.

FDA

3

- **To evaluate data, quality and integrity supporting a new drug or device application.**
- **Verify eletronic records, protection of human subjects (rights and welfare), financial documents, GMP, regulatory process is in compliance with applicable regulations.**

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

In June 2010 FDA issued a report called:

"Challenges to FDA ability to monitor and inspect foreign Clinical Trials" – the report found that Central and South America had the highest number of subjects per site and accounted for 26% of all subjects enrolled at foreign trial sites.

In 2008, the FDA inspected 1.9% of domestic clinical trial sites, while just 0.7% of foreign clinical trial sites were similarly audited.

Guidance: www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf

Why the site was selected to be inspected?

Reasons for inspections

- Routine surveillance
- " For Cause"
- Sensitive, medically or economically important new products

Reasons for Inspections

Medically or economically important new products.

- **Registration**

“ For Cause”

- **Informants.**
- **Suspecious.**
- **Information from other inspector.**
- **Safety or efficacy data is inconsistent with other study sites.**

Routine surveillance

- **To ensure that a site is complying with Protocol, SOP, GCP and applicable regulatory requirements.**

Reasons for Inspections

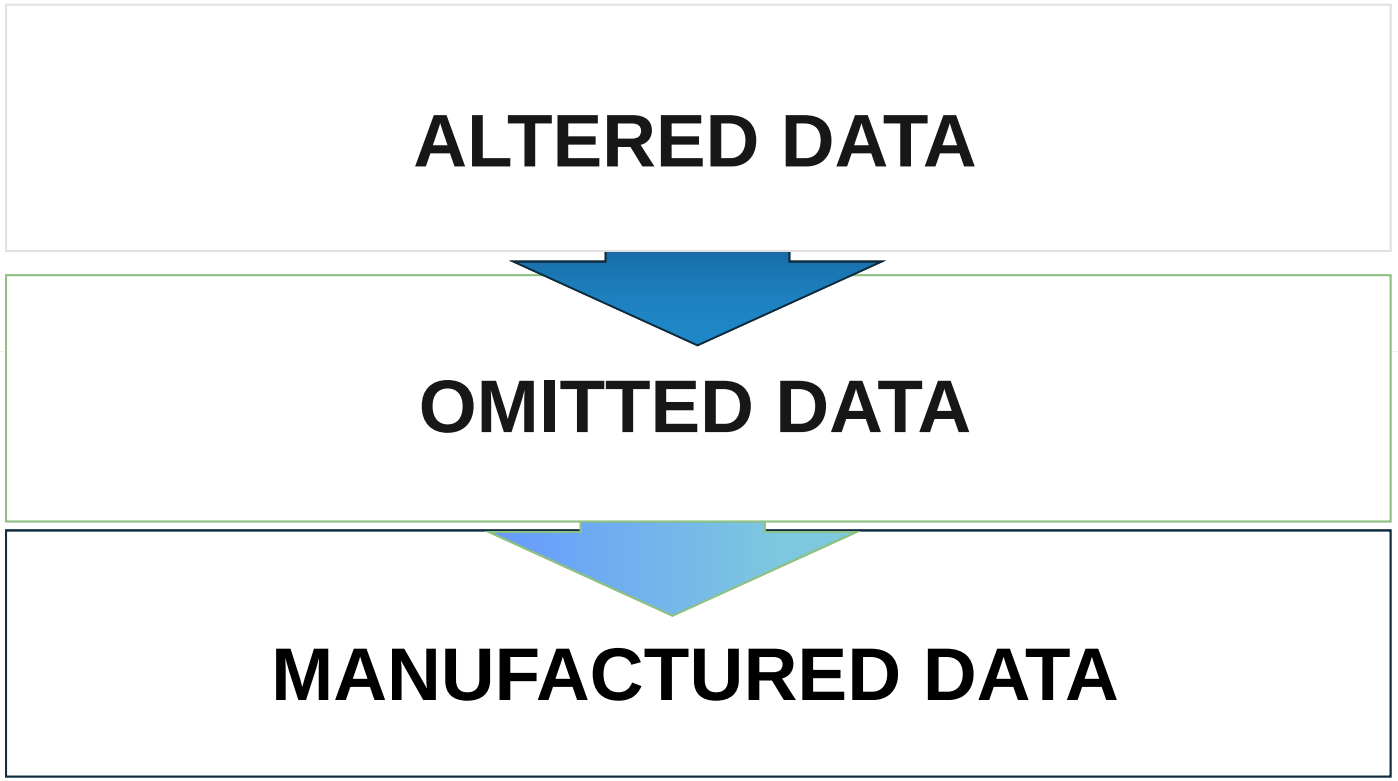
Factors Used to Choose a Site

- **Primary Efficacy X Support Protocols**
- **Pilot Sites X Other Sites**
- **High # of Subjects**
- **High # of Issues**
- **High # of SAEs**
- **High Staff Turnover**
- **Lack of Monitoring**

SOURCE DOCUMENT MUST BE ALCOA

1. **A**tributable
2. **L**egible
3. **C**ontemporaneous
4. **O**riginal
5. **A**ccurate (accurate information)

Types of Fraud



Indicators of Fraud

- Perfect diaries.
- Immaculate paper CRFs or no changes in the e-CRF / Source Documents.
- Perfect drug accountability records.

- Disappearing case documents.
- Miraculously appearing data.
- Drug taken exactly as prescribed.

- Use of the same pen.
- Questionable dates.
- Randomization before drug delivery.

-100% efficacy.
- No adverse event.s
- Fast recruitment.
- Identical blood tests.

Most Common Reasons for Regulatory Agencies to Reject a Study

- Source documentation not available for inspections.
- Failed to follow the protocol.
- Unreported concomitant medications that might interfere with evaluation of the drug.
- Un-reported AEs that could be associated with the study drug.

Preparing for an Inspection

Address Potential Vulnerabilities:

- **Correct data entry errors properly.**
  - **Never change original entries**
  - **Never re-copy original sources**
  - **Never backdate entries**
  - **Always cross out wrong entry with single line, write correct entry alongside, initial and date change.**

- **Where necessary, write addendum to the record.**

Preparing for an Inspection (cont.1)

Provide access to:

- Raw data (i.e lab equipments.)
- Source documents.
- eCRFs/CRF.
- Patient files.
- Personnel qualifications.
- Training files.

Do not provide:

- Personal records about employees other than qualifications.
- Sales and financial data.
- Other non study related records.
- Download of computers.

PREPARING FOR INSPECTION (cont.2)

<u>Upon arrival Regulatory Agency will</u>:

- **Clear security, recepcionist.**
- **Ask to see the person in charge (PI).**
- **Show credencials.**
- **Conduct a introductory interview.**

PREPARING FOR INSPECTION (cont.3)

PI informs...

PREPARING FOR INSPECTION (cont.4)

PI Should ...

- Confirm purpose of inspection.
- Inspector should not be permitted to mark any original document (only copies)
- Independent translator may be requested for international inspections
- Do not offer any information that is not explicity requested, only respond to specific questions !

PREPARING FOR INSPECTION (cont.6)

During Interviews:

- **Determine who did what (delegation).**
- **How were subjects recruited.**
- **How was IC process obtained.**
- **Where study procedures performed.**
- **How data was recorded.**
- **What were interactions with Sponsor / CRO.**
- **Status of study (screened, randomized, discontinued, SAEs, etc).**

Findings Classification: Audits & Inspections

Exemple of Critical Findings

- Ineligible patient enrolled in the study.
- Inadequate documentation to confirm eligiliblity of a patient enrolled in study.
- Many missed laboratory assessment for patient.
- Eligibility screening not done prior to dosing.
- Progress notes of PI and Sub-investigator don´t match (both claim to have performed physical explanation at certain visit).
- Patient received overdose of medication or expired medication.

Exemple of Major Findings

FDA 1572

- Sections not completed or completed incorrectly.

ICF

- The ICF of subjects enrolled obtained by sub-investigators or other person who are not listed in the delegation list.

Protocol Compliance

- Patient treated with IP not according to the protocol timeline.
- Vaccine, medication or infusion use different of stated in the protocol.
- Subjects were out of protocol specified window for randomization for various reasons.

Exemple of Major Findings (cont.)

Laboratory

- PI not reviewing abnormal results in timely manner.
- Missing lab results.
- Lab reports have not been sent to the site in a timely manner.

Source Document

- Missing vaccine, drug notes in SD.
- Incorrect dose administration sheet in SD.
- Exam report dates don´t correspond with exam procedure dates.
- No SD was present in the patient chart to confirm inclusion criteria.
- Adverse events not been properly documented in the medical charts.
- Adequate SD was not present.

Exemple of Major Findings (cont. 2)

ICH / GCP Compliance

- Perform any procedure or show any results of exam to satisfy inclusion criteria prior to signing informed consent.
- Patient signs document not approved by the IRB.
- The PI / Staff did not sign and date several SD entries.
- Protocol Amendments implemented prior regulatory approval.
- Physician completes questionaire, ICF by patient.

Exemple of Major Findings (cont. 2)

eCRF

- The eCRFs incomplete for several months.

Documentation of Investigator Study File

- Pending IMV follow up letters in the ISF.
- Discrepancy between the MVR date and follow-up letter.

IP Dose

- Incorrect vaccine or medication administration.

Closing Meeting

- The **inspector (s) should hold a closing meeting** with the inspected (s).
- Management board, if necessary, to ensure that the results of the inspection are **clearly understood** and that there is no misunderstanding by either the inspector(s) or the inspectee (s).
- Issues to be followed up by the inspectee (s) should be **addressed,** including **any additional documents** that may need to be sent to the inspection team.
- During this meeting the **inspector(s) should give details** on the circulation of inspection reports **(deadline to reply...)** according to the '*Procedure for reporting on GCP inspections, Regulatory Agencies and others, if applicable.*

References

- **ICH: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/integrated-addendum-good-clinical-practice.html**
- **WMA: http://www.wma.net/en/30publications/10policies/b3/**