VIII Congreso Colombiano de Investigación Clínica

Taller « Preparacion para Inspecciones y Auditorias »

Workshop « Preparation for inspections and audits »

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Disclaimer statement

The views expressed here are those of the author and do not necessarily represent or reflect the views of Sanofi Pasteur.

Preparation for inspections and audits

Presentation plan

Quality Assurance

- Definition
- Quality Assurance (QA) versus Quality Control (QC)

Audits

- Definition and objective
- Audit procedures
- Audit types
- Selection criteria for an audit
- Main topics reviewed during an audit
- Investigator site audit objectives, preparation, conduct, follow-up and closure

Inspections

- Definitions, objectives and types of inspections
- Inspections procedures: FDA – EMA - Comparison of manuals
- Guidance from other Regulatory Authorities
- Sponsor inspection preparation
- Sponsor organizational aspects
- Investigator site inspection preparation and progress

Audit versus Inspection

Conclusion

Preparation for inspections and audits

QUALITY ASSURANCE

Quality Assurance definition

ICH E6 – November 2016

1.46 Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

ICH E6 - R2 19
Nov 2016

Quality Assurance versus Quality Control

ICH E6 – November 2016

1.47 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.

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP and the applicable regulatory requirement(s).

Quality Assurance versus Quality Control

QUALITY CONTROL - QC
By Operations

Daily responsibility using systems to control the quality of ongoing activities

SYSTEMATIC

SAMPLING

QUALITY ASSURANCE - QA
Independent Audit

Evaluation of the control systems in place to ensure Quality

Quality Assurance versus Quality Control

- **Quality Assurance - QA**
  - Is independent from operational functions
  - Cannot be judge and jury
  - Is not directly involved in operational activities and decision-making
  - Evaluates Quality Control (QC) systems in place
  - QA activities are not on the critical path of processes
  - QA plays a consultation role:

    evaluation + advice + recommendation

Preparation for inspections and audits

AUDITS

Audit definition and objective
ICH E6 – November 2016

1.6 Audit

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, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).*

Audit definition and objective
ICH E6 – November 2016

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to ***evaluate trial conduct and compliance*** *with the protocol, SOPs, GCP, and the applicable regulatory requirements.*

Audit procedures
ICH E6 – November 2016

5.19.3 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the ***sponsor's written procedures*** *on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.*

(b) The sponsor's ***audit plan*** *and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).*

Audit procedures
ICH E6 – November 2016

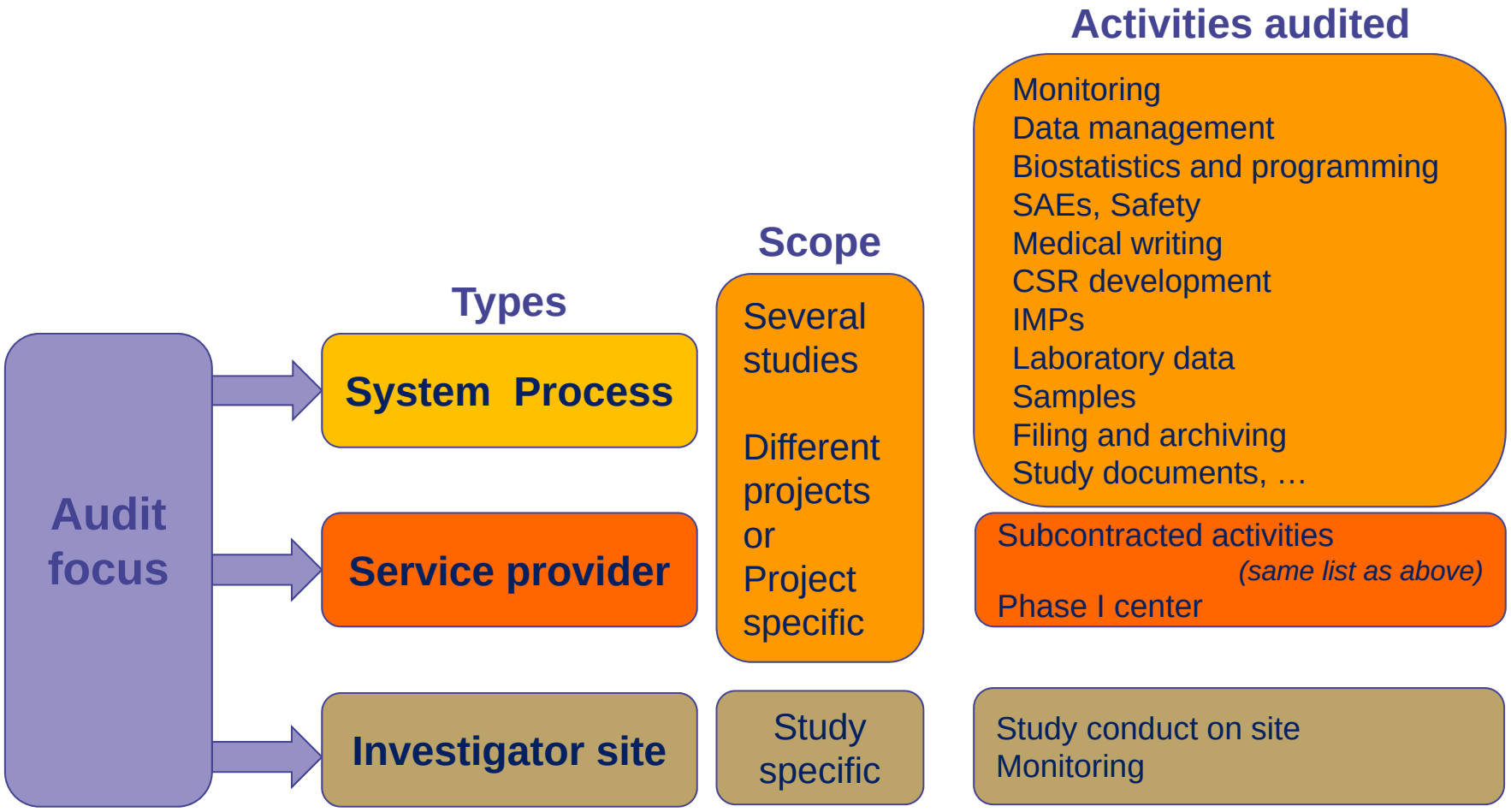
5.19.3 Auditing Procedures

*(c) The **observations and findings** of the auditor(s) should be documented.*

*(d) To preserve the **independence and value of the audit function**, the regulatory authority(ies) **should not routinely request the audit reports**. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.*

*(e) When required by applicable law or regulation, the sponsor should provide an **audit certificate**.*

Audit types


Activities audited
Scope
Types
Audit focus
System Process
Service provider
Investigator site
Several studies
Different projects or Project specific
Study specific
Monitoring
Data management
Biostatistics and programming
SAEs, Safety
Medical writing
CSR development
IMPs
Laboratory data
Samples
Filing and archiving
Study documents, …
Subcontracted activities
(same list as above)
Phase I center
Study conduct on site
Monitoring

Selection criteria for an audit

System / Process audit	Site / Study specific audit
Quality review on previous audits (trending analysis)	Pivotal study: based on development plan and registration strategy
Changes in procedures, processes, organization and responsibilities	Technical difficulties or technological specificities (non standard)
Important and high number of interactions in the whole process/system	Particular study design, primary evaluation criteria
Inspection observations	New country for the sponsor New investigator site for the sponsor New indication for the sponsor
	Vulnerable subjects population
Process identified as critical from an impact analysis on the global processes	Previous audit results on same study or previous studies on same project
Operation management's motivated request	Motivated request from sponsor clinical teams (deviations to protocol, GCP non compliances, difficult site…)

Main topics reviewed during an audit

Responsibilities	**Who does what, when, where and how?** ➢ Job description, organizational chart ➢ Line of communication ➢ Flow of products ➢ Facilities and equipment ➢ Decision making process…
Rules	**Are there Procedures and Working Instructions?** **Are they applied?**
Documentation	**Are activities described in writing?** **Is information collected documented in writing?** **Is traceability assured in order to reconstruct the events?**
Verification	**Is QC performed?**

Investigator site audit objectives

- Ensure the study is conducted in compliance with the protocol, ICH GCP guidelines, local and international regulations and the SOPs
- Ensure the subjects/patients are appropriately protected
- Evaluate whether the source documents and source data are **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal, **A**ccurate, **C**omplete (ALCOAC principle)
- Verify that the monitoring team adequately interacts between the sponsor and the investigator
- Give recommendations and advices for quality improvement purposes
- Prepare the site to Health Authorities inspections

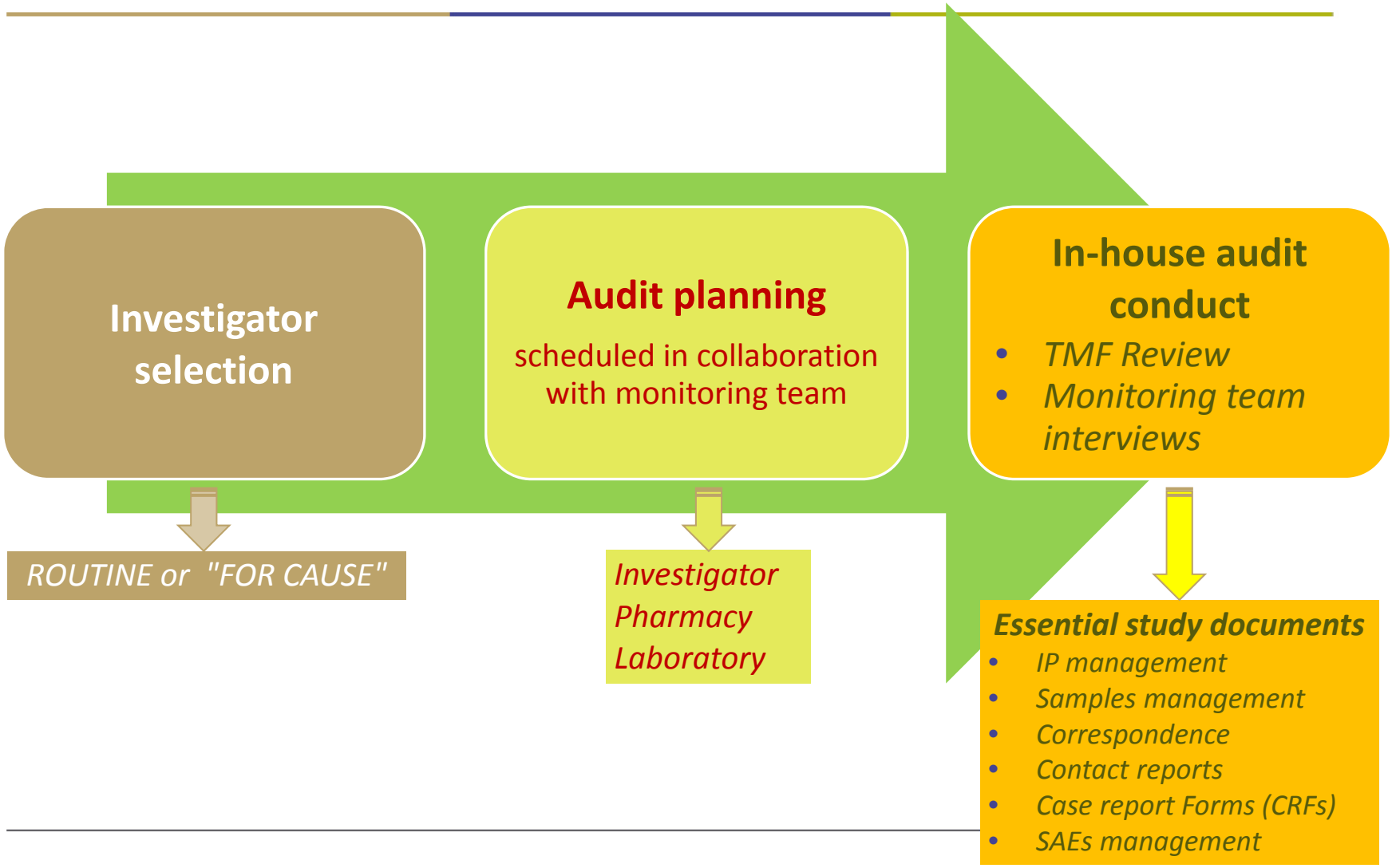
Two steps approach for an investigator site audit

In-house audit (Review of TMF, study data and events, personal records of monitoring team)

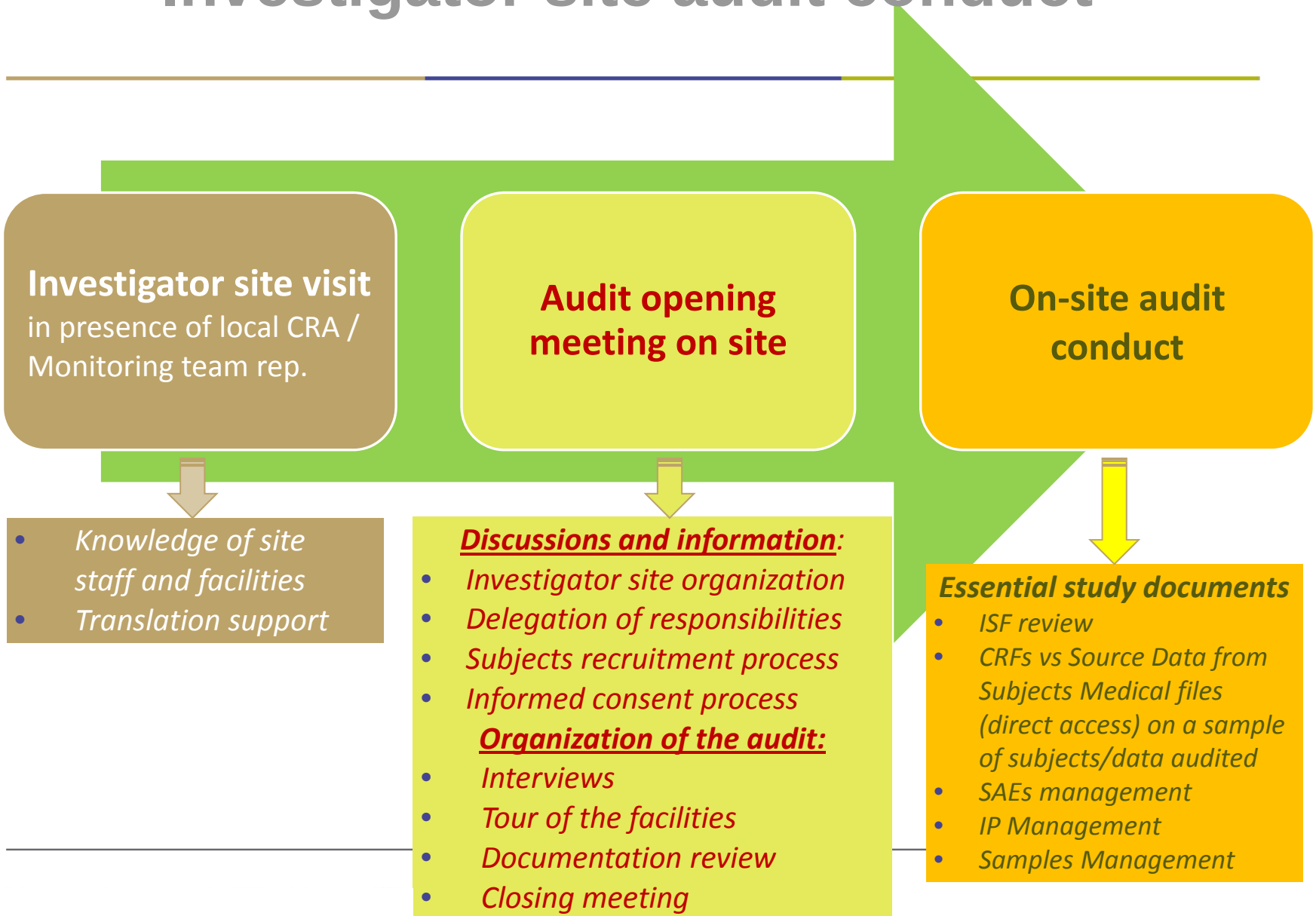
On-site audit with local CRA attendance

Auditees: monitoring team + investigator team

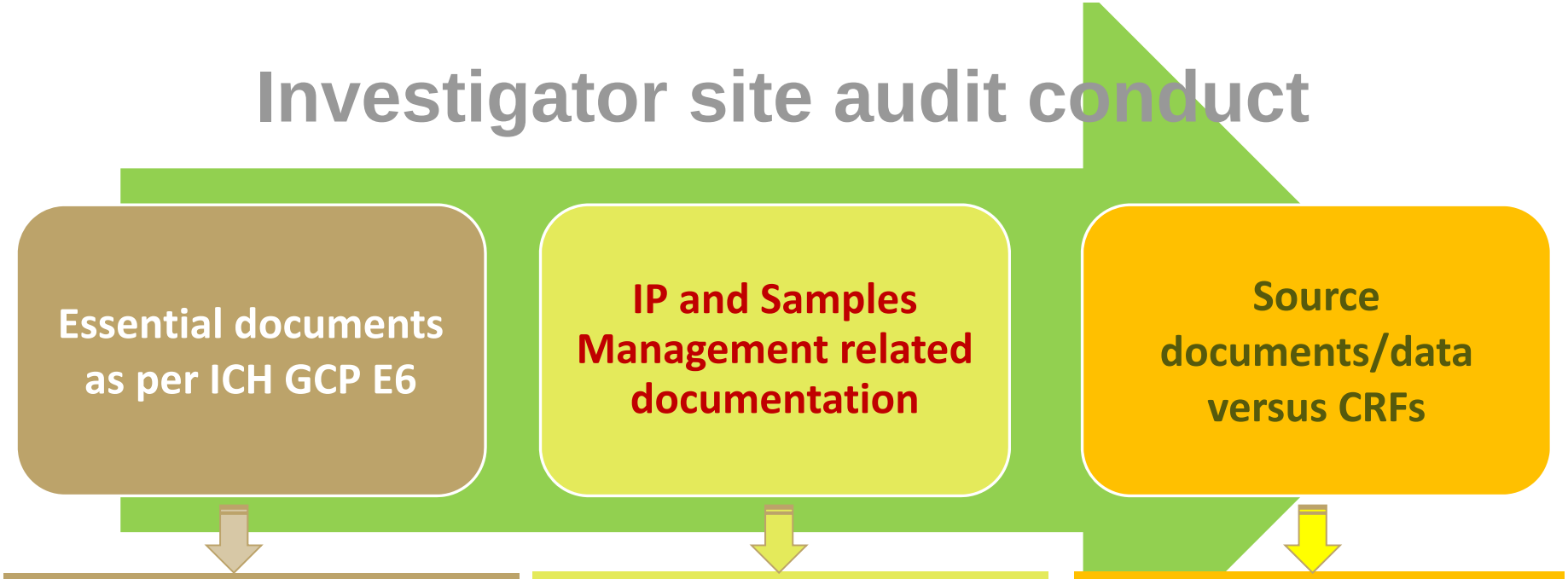
Investigator site audit preparation and in-house audit



Investigator site audit conduct



Investigator site audit conduct



Reference study documents:
- *Protocol, amendments, operating manuals, CRFs,…*

Investigator Brochure

Ethics Committee:
- *Composition, submissions and approvals*

Regulatory documentation:
- *Health Authorities*
- *Hospital/institution direction*

Signed ICFs

AEs and SAEs reporting

Site staff training

Study tasks delegation by PI

Laboratory normal value

…

Review of documentation:
- *IP Reception*
- *IP Accountability*
- *IP Expiry dates*
- *IP Randomization and double blind maintenance*
- *IP Dispensation*
- *IP Return accountability*
- *Samples collection*
- *Samples management*
- *IP and Samples Storage areas*
- *IP and Samples cold chain management*

Review of subjects Medical files
- *Subjects history*
- *Subjects eligibility: inclusion/exclusion criteria*
- *Clinical examination data*
- *Laboratory data*
- *Previous, associated and concomitant treatments*
- *Adverse events documentation and reporting timelines*
- *Source data transcription accuracy*
- *Study Documents maintenance , filing and archiving*

Audit follow-up and closure

Closing Meeting
On-site + In-house

From Initial to Final Audit report

CAPAs follow-up and audit closure

<u>At the end of the audit:</u>
- *To present audit results*
- *To clarify misunderstandings*

<u>Initial audit report</u>
- *Sent to the Monitoring team one month after the audit conduct*

<u>Debriefing meeting</u>
With the Monitoring team :
- *for clarification if needed*
- *for agreement on corrective and preventive action plans CAPAs*

<u>Final audit report</u>
Integrating agreed CAPAs
Sent to sponsor auditees, clinical team and Managers

<u>CAPAs follow-up</u>
- *Auditees in charge of CAPAs inform auditors of CAPAs implementation*
- *Auditors check and close CAPAs and observations*

<u>Audit closure</u>
- *Once all CAPAs are closed, Auditors close the audit.*

Pause 1

Preparation for inspections and audits

INSPECTIONS

Definitions – Objectives and Types

ICH - Inspection definition

ICH E6 – November 2016

1.29 Inspection

The **act by a regulatory authority of conducting an official review** of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

EMA Inspection definition

DIRECTIVE 2001/20/EC

The ***act by a competent authority of conducting an official review*** of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect.

FDA Inspection definition

COMPLIANCE PROGRAM GUIDANCE MANUAL (CPGM) - Chapter 48

The objectives of the BIMO Program* are:

* *Bioresearch Monitoring Program*

- To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;
- To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and
- To assess compliance with FDA's regulations governing the conduct of clinical trials.
- The purpose of this compliance program is to provide instructions to the field and Center personnel for conducting inspections of sponsors, contract research organizations (CROs), and monitors, and recommending associated administrative/enforcement actions.

Inspection objectives and types

Objective of a GCP inspection

- Verify that studies were conducted according to GCP, regulations, protocol and related documents and that the data are reliable and verifiable

Types of GCP inspections

- Pre Approval Inspection (PAI)
- Sponsor inspection
- Investigator site inspection
- Contract Research Organizations (CROs) inspection
- Bioequivalence inspection (clinical & bio-analytical part)

Preparation for inspections and audits

INSPECTIONS

Procedures

Inspection procedures

EMA procedures and guidance for GCP inspections

Coordination, preparation, conduct, reporting of:

- Routine inspections
- Inspections triggered by issues arising during the assessment of the dossier or by other information such as previous inspection experience.

- Usually requested during initial review of a Marketing Authorisation Application
- Could arise post-authorisation

- Investigator site
- Sponsor and CRO
- Clinical Laboratories
- Computerized Systems
- Phase I units

EMA GCP Inspections procedures

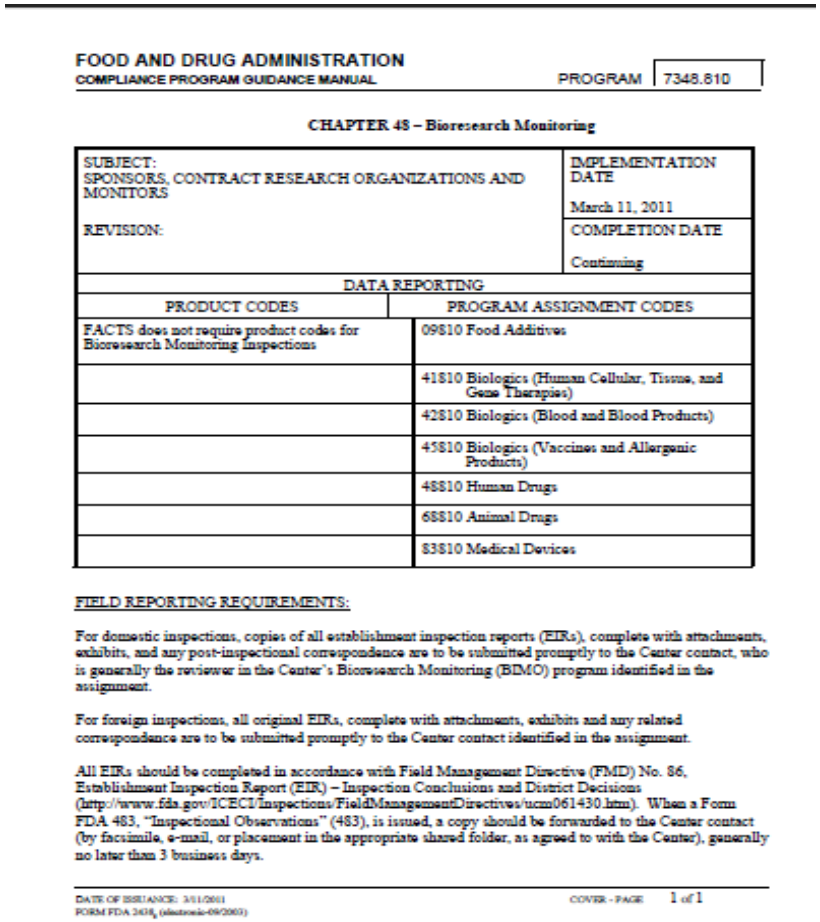
FDA Compliance Program Guidance Manual (CPGM)

CPGM details the inspection process : who, what, how
In **Bioresearch Monitoring (BIMO) Compliance Programs – Chapter 48**

Program #	Compliance program
7348.001	In vivo Bioequivalence
7348.808	Non clinical laboratories
7348.809	IRB
7348.810	Sponsors, CROs and Monitors
7348.811	Clinical Investigators
…	

FDA Compliance Manuals

Inspection procedures
FDA Compliance Program Guidance Manual



FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM GUIDANCE MANUAL
PROGRAM 7348.810

CHAPTER 48 – Bioresearch Monitoring

SUBJECT: SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS	IMPLEMENTATION DATE March 11, 2011
REVISION:	COMPLETION DATE Continuing

DATA REPORTING	
PRODUCT CODES	PROGRAM ASSIGNMENT CODES
FACTS does not require product codes for Bioresearch Monitoring Inspections	09810 Food Additives
	41810 Biologics (Human Cellular, Tissue, and Gene Therapies)
	42810 Biologics (Blood and Blood Products)
	45810 Biologics (Vaccines and Allergenic Products)
	48810 Human Drugs
	68810 Animal Drugs
	83810 Medical Devices

FIELD REPORTING REQUIREMENTS:

For domestic inspections, copies of all establishment inspection reports (EIRs), complete with attachments, exhibits, and any post-inspectional correspondence are to be submitted promptly to the Center contact, who is generally the reviewer in the Center's Bioresearch Monitoring (BIMO) program identified in the assignment.

For foreign inspections, all original EIRs, complete with attachments, exhibits and any related correspondence are to be submitted promptly to the Center contact identified in the assignment.

All EIRs should be completed in accordance with Field Management Directive (FMD) No. 86, Establishment Inspection Report (EIR) – Inspection Conclusions and District Decisions (http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm061430.htm). When a Form FDA 483, "Inspectional Observations" (483), is issued, a copy should be forwarded to the Center contact (by facsimile, e-mail, or placement in the appropriate shared folder, as agreed to with the Center), generally no later than 3 business days.

DATE OF ISSUANCE: 3/11/2011 COVER - PAGE 1 of 1
FORM FDA 2438 (electronic-09/2003)

- Chapter 48: Bioresearch Monitoring
- Inspection of Sponsors, CRO and Monitors
- **Part III – Inspectional**
  - Sections C – L
  - Sections M – S, as applicable
- A copy can be obtained through the web address below:
  - http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133770.pdf

Inspection procedures
FDA Sponsor / CRO inspection scope (1/2)

- An FDA Inspection will include the following topics per the manual:
  - A and B are general information about inspection procedure
  - C. Organization and Personnel
  - D. Registration of Studies on Clinicaltrials.gov
  - E. Selection and Monitoring of Clinical Investigators
  - F. Selection of Monitors
  - G. Monitoring Procedures and Activities
  - H. Quality Assurance (QA)
  - I. Safety/Adverse Event Reporting
  - J. Data Collection and Handling
  - K. Record Retention
  - L. Financial Disclosure

Were records kept for the right period of time?

Inspection procedures
FDA Sponsor / CRO inspection scope (2/2)

- An FDA Inspection will include the following topics per the manual: (as applicable)

M. Electronic Records and Electronic Signature

N. Test Article — = Investigational products

O. Devices

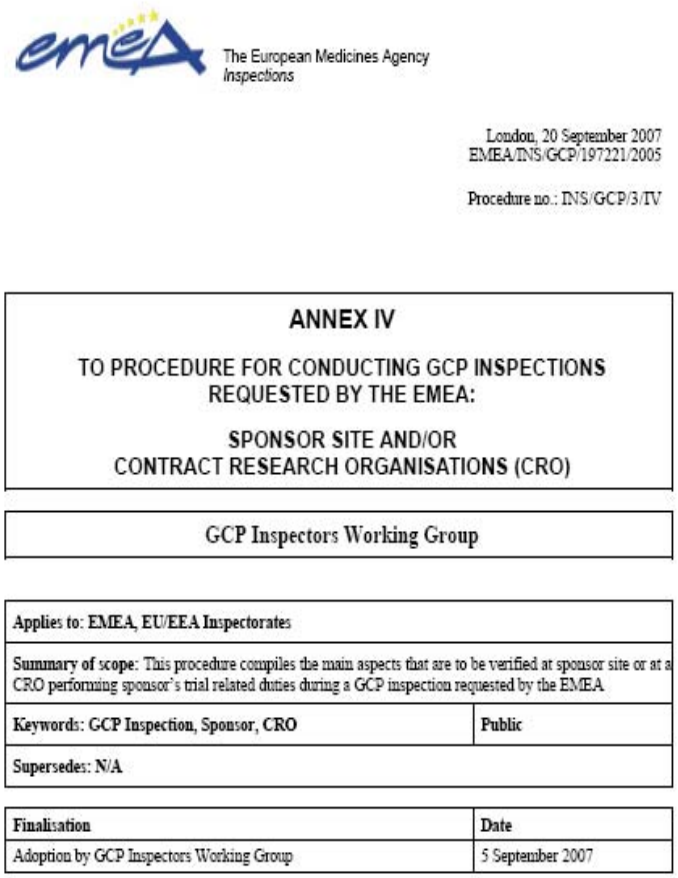
P. Emergency Research — Studies described in 21 CFR 50.24 in which an IRB may approve an investigation without requiring ICF

Q. International Data – Human Drugs and Biologics — Refers to:
- US site inspected by non-US Health Authority
- Non-US site inspected by FDA

R. Nonclinical Laboratory Studies — Only applicable to nonclinical studies

S. Sample Collection

Inspection procedures
EMA Sponsor / CRO inspection



The European Medicines Agency
Inspections

London, 20 September 2007
EMEA/INS/GCP/197221/2005

Procedure no.: INS/GCP/3/IV

ANNEX IV

TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE EMEA:

SPONSOR SITE AND/OR
CONTRACT RESEARCH ORGANISATIONS (CRO)

GCP Inspectors Working Group

Applies to: EMEA, EU/EEA Inspectorates	
Summary of scope: This procedure compiles the main aspects that are to be verified at sponsor site or at a CRO performing sponsor's trial related duties during a GCP inspection requested by the EMEA	
Keywords: GCP Inspection, Sponsor, CRO	**Public**
Supersedes: N/A	

Finalisation	**Date**
Adoption by GCP Inspectors Working Group	5 September 2007

- INS-GCP-3 Annex IV "Procedure for conducting GCP inspections requested by the EMA- Sponsor Site and/or CRO"

- A copy can be obtained through the web address below:
  - **http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004470.pdf**

Inspection procedures
EMA Sponsor / CRO inspection scope

- EMA Inspection will include the following topics per the manual:
  - **Organization and Personnel**
  - **Facilities and equipment**
  - **Sponsor/CRO Operation Procedures**
  - **Implementation and termination of the Clinical Trial**
  - **Monitoring**
  - **Investigational Medicinal Product**
  - **Safety and adverse events reporting**
  - **Data handling and clinical trial report (CTR)**
  - **Clinical trial documentation and archiving**
  - **Audit**

Comparison of manuals – Sponsor/CRO inspection

EMA inspection will include the following topics per the manual :	Corresponding Section in FDA Compliance Manual:
2.1 Organization and Personnel	C) Organization and Personnel
2.2 Facilities and equipment	M) Electronic Records & Signatures
2.3	
3.1 Clinic	
3.2 M	
3.3 Investigational Medicinal Product	N) Test Article
3.4 Safety and adverse events reporting	I) Safety/Adverse Event Reporting
3.5 Case Report Form data verification	J) Data Collection and Handling
3.6 Data handling and clinical trial report (CTR)	
3.7 Clinical trial documentation and archiving	K) Record retention
3.8 Audit	H) Quality Assurance

The EMA topics are covered in the FDA Compliance Manual, just in a different order.

However, there are additional FDA topics: US-specific items, topic-specific

- D) Registration of Studies on Clinicaltrials.gov
- L) Financial Disclosure
- O) Devices
- P) Emergency research
- Q) International Data – Human Drugs and Biologics
- R) Nonclinical Laboratory Studies

Inspection procedures
FDA Compliance Program Guidance Manual

FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM GUIDANCE MANUAL PROGRAM 7348.811

PROGRAM 7348.811

CHAPTER 48- BIORESEARCH MONITORING

CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS

Date of Issuance: December 8, 2008

Guidance for FDA Staff

SUBJECT: Clinical Investigators and Sponsor Investigators	IMPLEMENTATION DATE December 8, 2008
REVISION:	COMPLETION DATE Continuing

DATA REPORTING	
PRODUCT CODES	PROGRAM ASSIGNMENT CODES
FACTS does not require product codes for Bioresearch Monitoring Inspections	09811 Food Additives
	41811 Biologics (Cell; Gene Transfer)
	42811 Biologics (Blood)
	45811 Biologics (Vaccines)
	48811 Human Drugs
	68811 Animal Drugs
	83811 Medical Devices

- Chapter 48: Bioresearch Monitoring
- Inspection of clinical investigators
- **Part III – Inspectional**
  - **Sections C – R**
- A copy can be obtained through the web address below:
  - **http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133773.pdf**

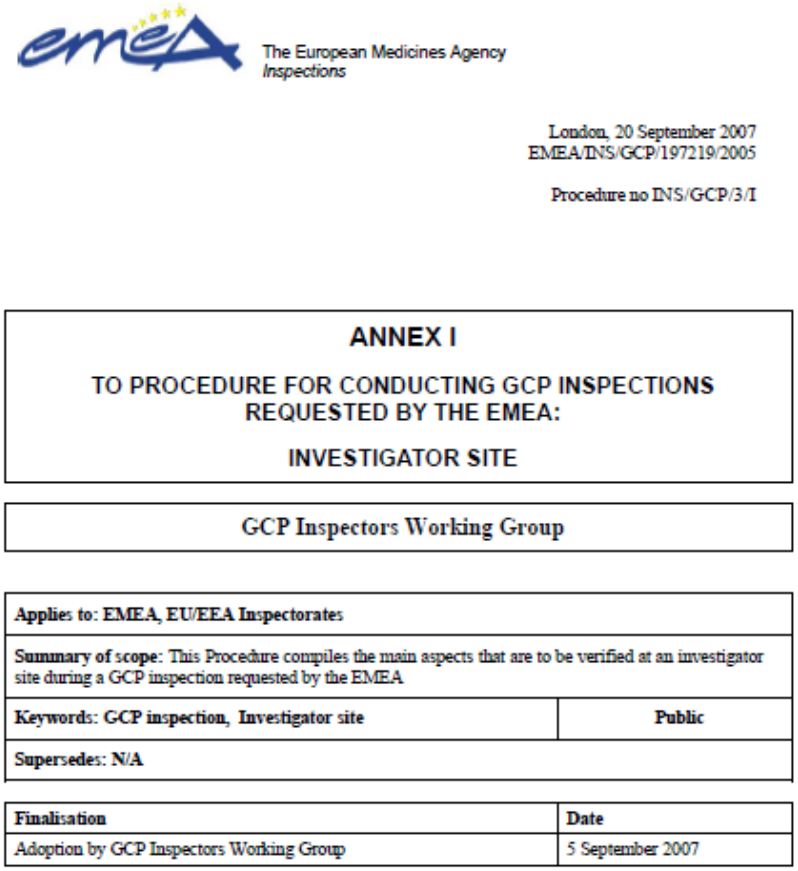
Inspection procedures
FDA Clinical Investigator inspection scope (1/2)

- An FDA Inspection will include the following topics per the manual:
  - **C. Authority and administration for studies involving human drugs, biologics, and devices**
  - **D. Protocol for human drug, biologic or device study**
  - **E. Institutional review board (IRB) for human drug, biologic or device study**
  - **F. Human subjects' records**
  - **G. Other study records**
  - **H. Financial disclosure**
  - **I. Electronic records and electronic signatures**

Inspection procedures
FDA Clinical Investigator inspection scope (2/2)

- An FDA Inspection will include the following topics per the manual:
  - **J.** Test article control — IP accountability, dispensation, storage
  - **K.** Records custody and retention — Records retention according to protocol and 21CFR
  - **L.** Reports to sponsor — Records/reports submission to sponsor as per protocol
  - **M.** Monitoring
  - **N.** Animal clinical studies — For animal new drugs
  - **O.** Device studies
  - **P.** Establishments inspection reports (EIRs) — Inspection report for a particular site
  - **Q.** International inspections — Refers to:
    - US site inspected by non-US Health Authority
    - Non-US site inspected by FDA
  - **R.** Sample collection

Inspection procedures
EMA Investigator Site inspection



The European Medicines Agency
Inspections

London, 20 September 2007
EMEA/INS/GCP/197219/2005

Procedure no INS/GCP/3/I

ANNEX I

TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE EMEA:

INVESTIGATOR SITE

GCP Inspectors Working Group

Applies to: EMEA, EU/EEA Inspectorates	
Summary of scope: This Procedure compiles the main aspects that are to be verified at an investigator site during a GCP inspection requested by the EMEA	
Keywords: GCP inspection, Investigator site	**Public**
Supersedes: N/A	

Finalisation	**Date**
Adoption by GCP Inspectors Working Group	5 September 2007

- INS-GCP-3 Annex I "Procedure for conducting GCP inspections requested by the EMA – Investigator site"

- A copy can be obtained through the web address below
  - **http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004458.pdf**

Inspection procedures
EMA Investigator Site inspection scope

- EMA Inspection will include the following topics per the manual:
  - **Legal and administration aspects**
  - **Organisational aspects:**
    - Implementation of the trial at the site
    - Facilities and equipment
    - Management of biological samples
    - Organisation of the documentation
    - Monitoring and auditing
    - Use of computerised system
  - **Informed consent of trial subject**
  - **Review of the trial subject data**
  - **Management of the investigational medicinal product(s)**

Comparison of manuals – Investigator Site inspection

EMA inspection will include the following topics per the manual :	Corresponding section in FDA Compliance Manual:
2. Legal and administration aspects	E) Institutional review board (IRB) for human drug, biologic or device study
3. C	C) Authority and administration f… s involvi… vices
	…vice
	…res
	…retention
	M) Monitoring
	R) Sample collection
4. Informed consent of trial subjects	F) Human subjects' records
5. Review of the trial subject data	D) Protocol for human drug, biologic or device study
6. Management of the IMP	J) Test article control

The EMA topics are covered in the FDA Compliance Manual, just in a different order.

Relations with authorities are dispatched throughout the FDA guide.

However, there are additional FDA topics: US-specific items, topic-specific

- H) Financial disclosure
- N) Animal clinical studies
- O) Device studies
- P) Establishments inspection reports (EIRs)
- Q) International inspections

Preparation for inspections and audits

INSPECTIONS

Guidances from other Regulatory Authorities

Guidances from other Regulatory Authorities

Countries	Website of HA, inspection guidance
Australia	http://www.tga.gov.au No inspection manual identified
Brazil	http://www.anvisa.gov.br Boas Práticas Clínicas: Documento das Américas – Annexo 4 http://www.anvisa.gov.br/medicamentos/pesquisa/boaspraticas_americas.pdf
China	CFDA – Regulatory Guide http://eng.sfda.gov.cn/WS03/CL0755/
Colombia	https://www.invima.gov.co No inspection manual identified
Honduras	http://www.dgrs.gob.hn No inspection manual identified
Indonesia	http://www.pom.go.id/new/index.php/home/en No inspection manual identified

Guidances from other Regulatory Authorities

Countries	Website of HA, inspection guidance
Japan	PMDA https://www.pmda.go.jp/english/review-services/index.html No GCP inspection manual identified
Malaysia	http://www.bpfk.gov.my Guidelines for Good Clinical Practice (GCP) Inspection: http://portal.bpfk.gov.my/view_file.cfm?fileid=909
Mexico	http://www.cofepris.gob.mx Refer to Buenas Prácticas Clínicas: Documento das Américas – Annexo 4 http://www.anvisa.gov.br/medicamentos/pesquisa/buenaspracticas_espanol.pdf
Philippines	http://www.fda.gov.ph No inspection manual identified
Singapore	http://www.hsa.gov.sg Guideline on GCP Compliance Inspection Framework: http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Clinical_Trials/Overview/Regulatory_Guidelines.html
Thailand	http://www.fda.moph.go.th/eng/index.stm No inspection manual identified

Pause 2

Preparation for inspections and audits

INSPECTIONS

Sponsor preparation

How to prepare yourself

Preparation for **all** sponsor departments

Job Description, CVs, qualifications, training matrix/records

Organization charts

List of SOPs

- current and effective per trial
- per department

Preferred partners/CRO

- List of CROs per trial
- Availability of a presentation describing:
  - CRO selection process
  - WOTL and contracted activities
  - CRO oversight and trainings
- List of SOPs used by CROs per trial

Who will face an inspector?

Subject Matter Expert (SME)	• **Is an expert on specific activities, tools, processes…** • **Should have a back-up available**
In front of inspectors, SME	• **Knows the scope of his/her activities** • **Can explain them clearly** • **Is prepared to answer inspectors questions** • **Examples follow…**

Sponsor departments involved

Clinical department

- Monitoring
- Clinical Development
- Medical Writing
- Translation
- Clinical Documentation
- Clinical Data Manager
- Biostatistics

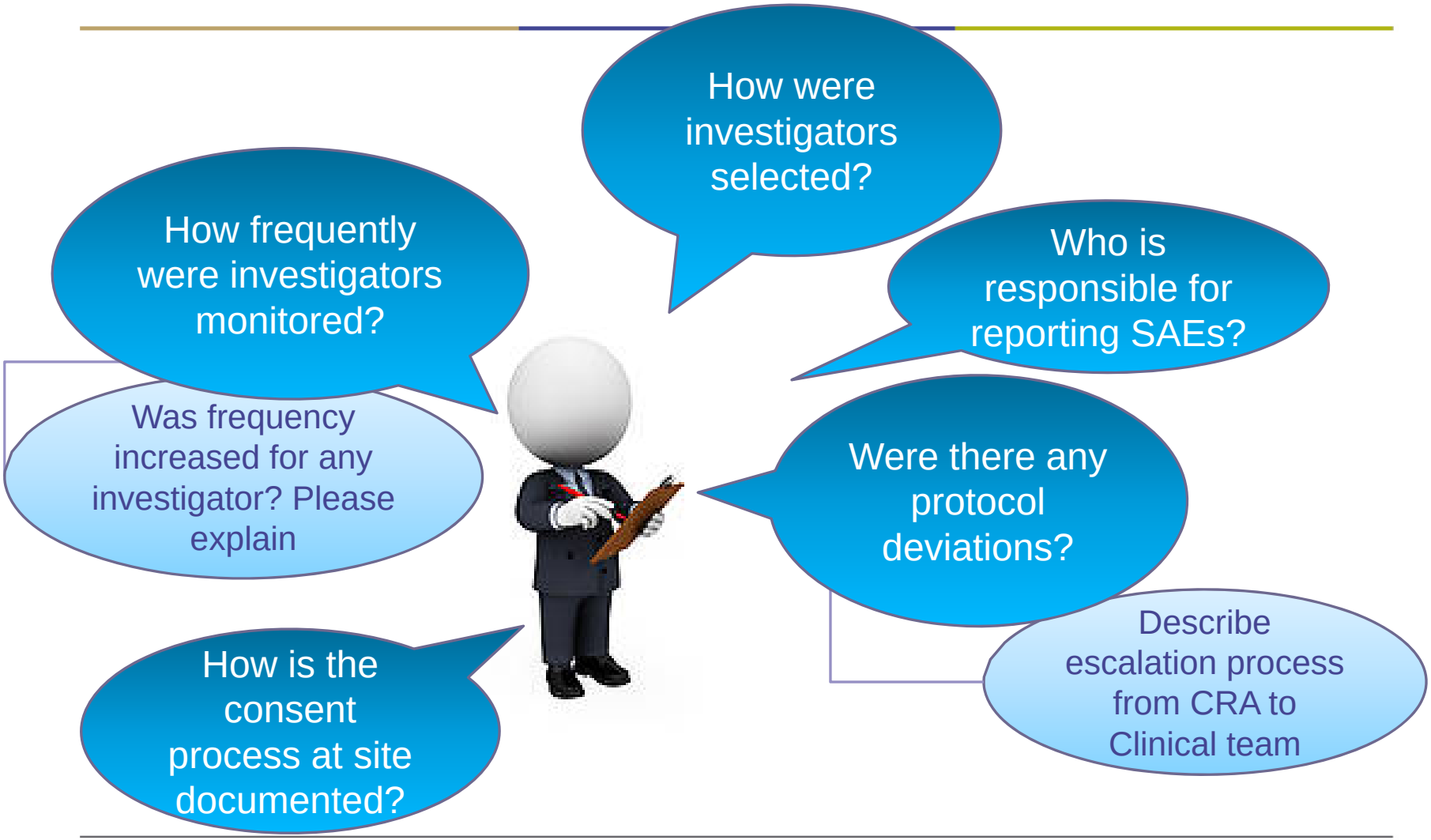
Pharmacovigilance - PV

Regulatory Affairs - RA

Clinical Supply Chain - CSC

Central Laboratory

Clinical dept. – Monitoring



Clinical dept. – Monitoring
Ethics Committee & Health Authorities

Describe the submission process of SAEs to EC/HA

Describe ICF submission to EC/IRB

How were protocol deviations reported to EC/IRB/MoH?

Clinical dept. – Monitoring
IP management

Describe IP management

Does the IP require any preparation, manipulation or processing at the investigator site?

How were the instructions provided to the investigator sites?

How was this activity assessed to ensure full compliance?

Were there any temperature deviations reported?

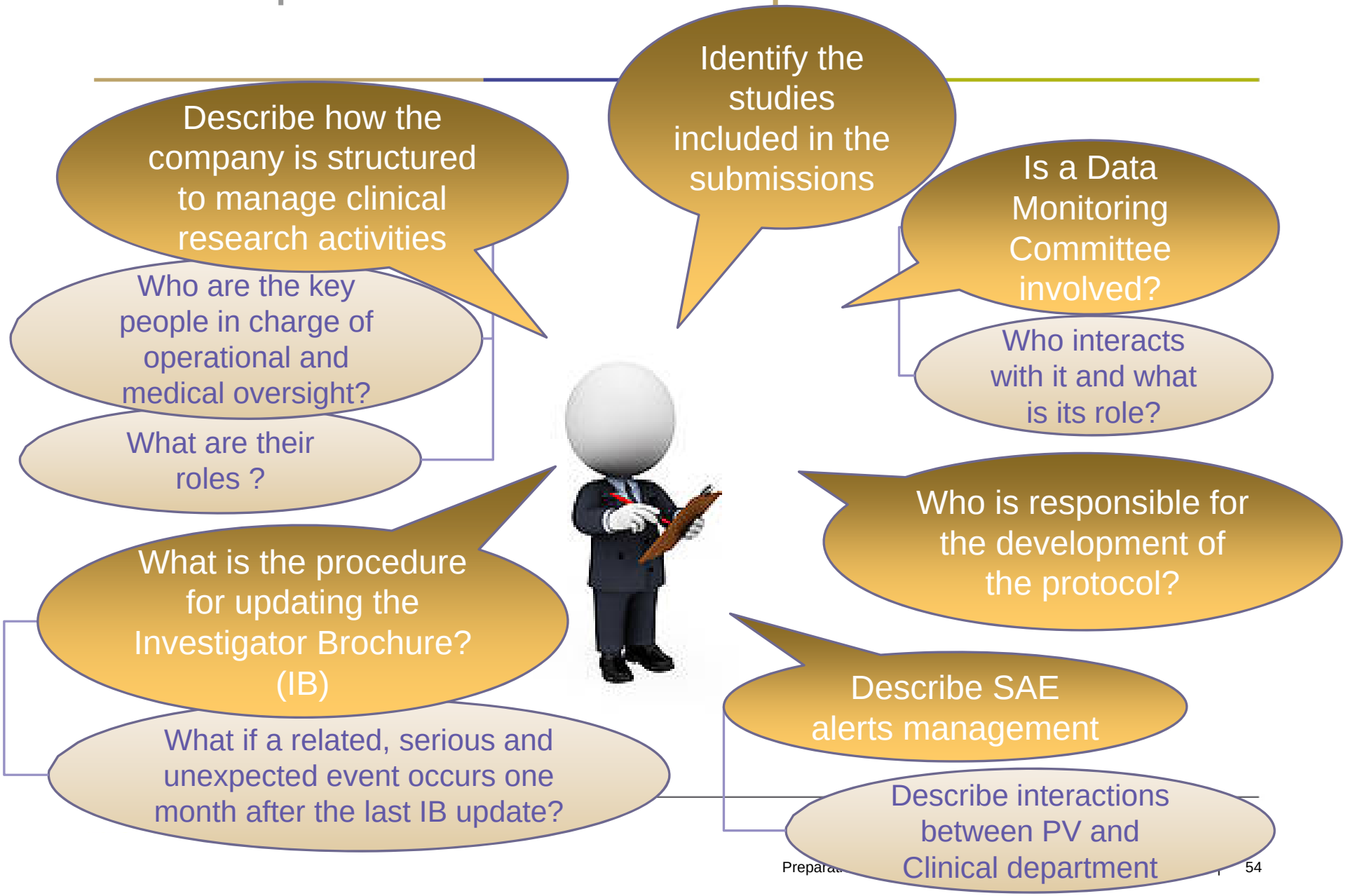
At site?

During shipment?

How do you ensure that blind is maintained?

Are records available to demonstrate the final disposition of the IP?

Clinical dept. – Clinical Development



Clinical dept. – Medical Writing

The following questions may concern protocol, ICF, IB, CSR and CTD

What is the document development process?

Describe the production of the document

How are documents approved?

Describe the management of amendments

Do you QC these documents and how is it documented?

What is the role of a medical writer vs an electronic document specialist?

Clinical dept. – Translation

Describe the process for study documents translation

Is there a QC process of translated documents?

How is it documented?

Explain the translators selection process. (vendors, freelance)

How are the needs for translation of study documents evaluated?

What happens if an external translator provides a bad translation?

How do you identify a translation in edoc?

In which situation would Translation not be involved?

Clinical dept. – Clinical Documentation

Describe how the company is structured to manage TMF activities

Describe the role and responsibilities of ClinDoc Personnel

Is ClinDoc staff a member of the Clinical Team?

Is ClinDoc staff listed in the sponsor staff list?

Can you describe the transition from paper to electronic TMF?

How did you ensure the consistency between paper and electronic documents?

Describe the process for TMF QC activities

Clinical dept. – Clinical Data Management

How does Clinical Data Management work within the Clinical Team?

Can you describe the query process

How do you identify and obtain additional information from sites on reported events?

How do you confirm closure of all queries?

Describe the process for the eCRF creation and update

Describe lock/unlock process

If any unlock, what were the reasons?

Is there a business continuity / disaster recovery plan (Database crash, eData -Capture (EDC) problem)?

Describe Clinical Data Management roles

Clinical dept. – Biostatistics

Describe interactions with the CRO liaising with IDMC for the transfer of:

- the randomization list at the beginning of the trial
- Data for each meeting

Describe the randomization process

- How is blind maintained?

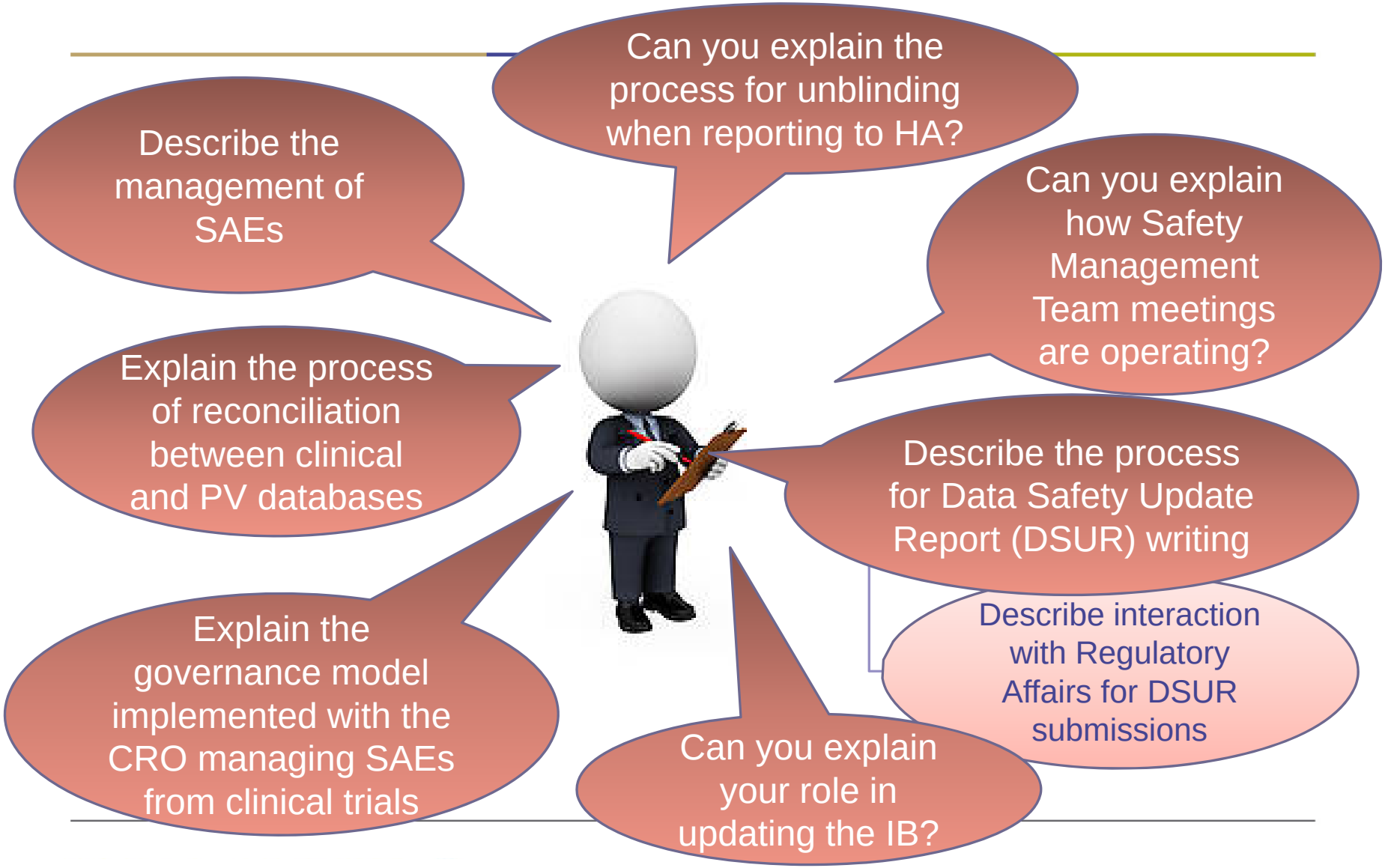
Please provide more details about the statistical environment used

When was the CDM database locked?

Can you explain interactions with Clinical Data Management?

Describe roles and functions within Biostatistics

Pharmacovigilance PV



Regulatory Affairs - RA

Were there trials performed that were not included in the submission?

Why were they not included?

Which HA submissions are you in charge of?

Are there studies under IND?

Can you explain your role in the submission of Data Safety Update Reports (DSUR)?

Clinical Supply Chain

To what location were the unused IP returned at the end of an investigator's participation / end of study?

Who is responsible for developing the labeling text?

Who has final approval on the labeling text?

Describe the flow of IP from the manufacturing site to receipt by the local depot

Describe the packaging process
(How? Where?)

Can global IP accountability be fully reconciled with available documentation?

Central Laboratory

Describe the process of data transfer / reconciliation to the clinical database

How do you manage sample identification reconciliation issue?

How do you select external laboratories?

How do you oversee their activities?

How do you make sure that a subject agrees to have his samples processed?

How do you ensure the laboratory is blinded?

How do you ensure that laboratory technicians are trained to perform the test?

Preparation for inspections and audits

INSPECTIONS

Sponsor organizational aspects

Preparation of inspectors arrival

Warn reception desk and security about inspectors' arrival

- Ensure inspectors identities will be verified
- Ensure the inspection team leader (QA) is alerted upon inspectors arrival

Inspection team leader (QA) meets the inspectors

- Ensure inspection track is determined in advance and followed as planned
- Ensure offices and desks on inspectors path are clean, offices doors are closed (clean desk policy)

Never leave the inspectors alone

- Prepare a list of persons who will have lunch with inspectors
- Ensure inspectors have no direct contact with other collaborators

Rooms for interviewees

- Ensure rooms are booked for interviewees coming from different sponsor sites than the site hosting the inspection
- Ensure the war room is not overcrowded

Why prepare organizational aspects?

Limit inspector comes and goes on site

Have interviewees available on time

Have documents quickly available

Inspection room team

Team Leader (QA)

- **Coordinates the inspection team**
- **Writes document requests, queries…**
- **Ensures all requests by inspectors have been addressed**
- **Facilitates interaction with inspectors**
- **Prepares daily summaries**
- **Escorts the inspector**

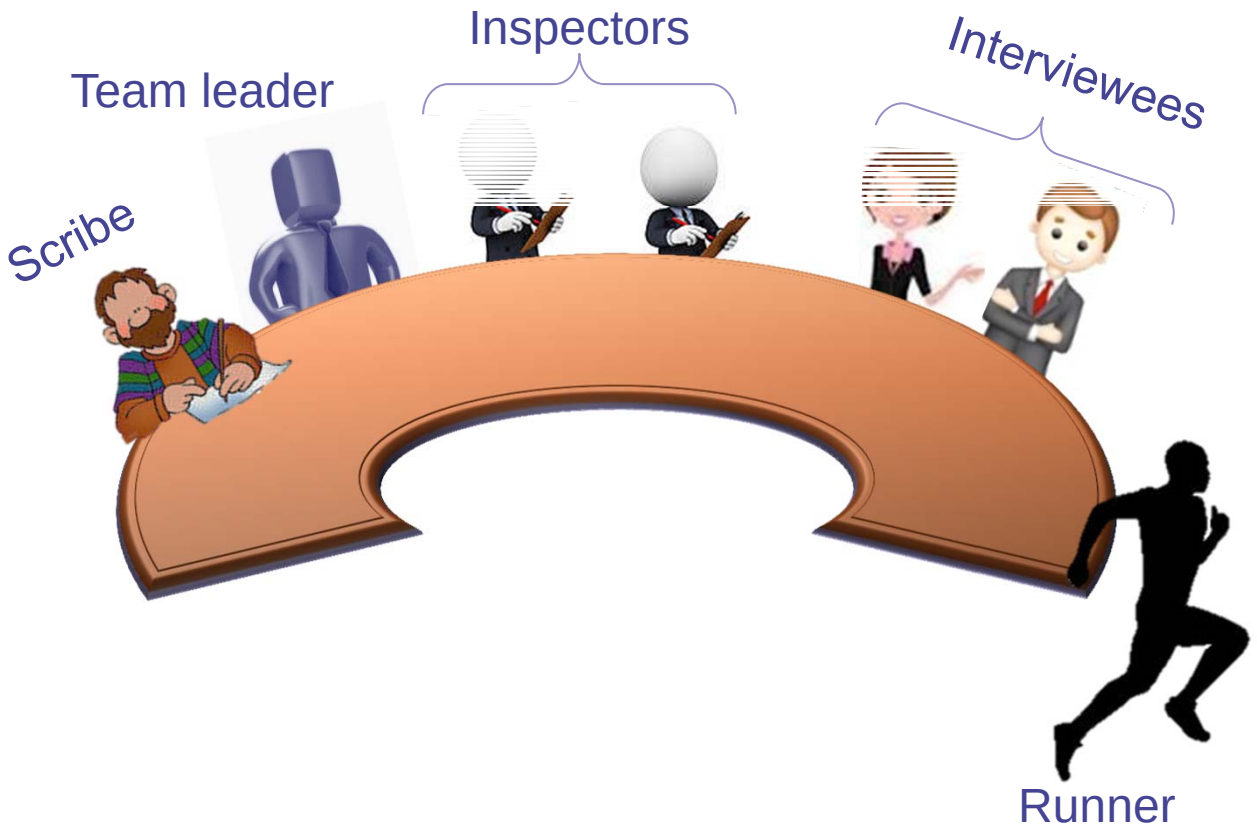
Runner

- **Is in inspection room**
- **Liaises between inspection room and war room**
- **Informs the war room of any information and context regarding requests**

Scribe

- **Records all questions, comments, concerns, and observations made by inspectors**
- **Records all responses made by interviewees**
- **Records all information and documents requested and reviewed by inspectors**
- **Helps with daily summaries**

Inspection room (IR)



- If inspectors split, provide space for each team
- The sponsor needs to anticipate an inspection team for each group of inspectors

War room

Example of an inspection room organization

War room (WR)

- War room = back room = stage room
  - **If several inspection teams in IR, same organization in WR**
  - **Have a war room leader (QA) for each inspection team**
  - **Every document/person goes through the WR before entering IR**

Administrative Support

- **Prints, copies, staples, stamps and logs all documents provided to inspector**
- **Maintains an overview of status requests** (paperboard, eroom…)

Document Coordinator

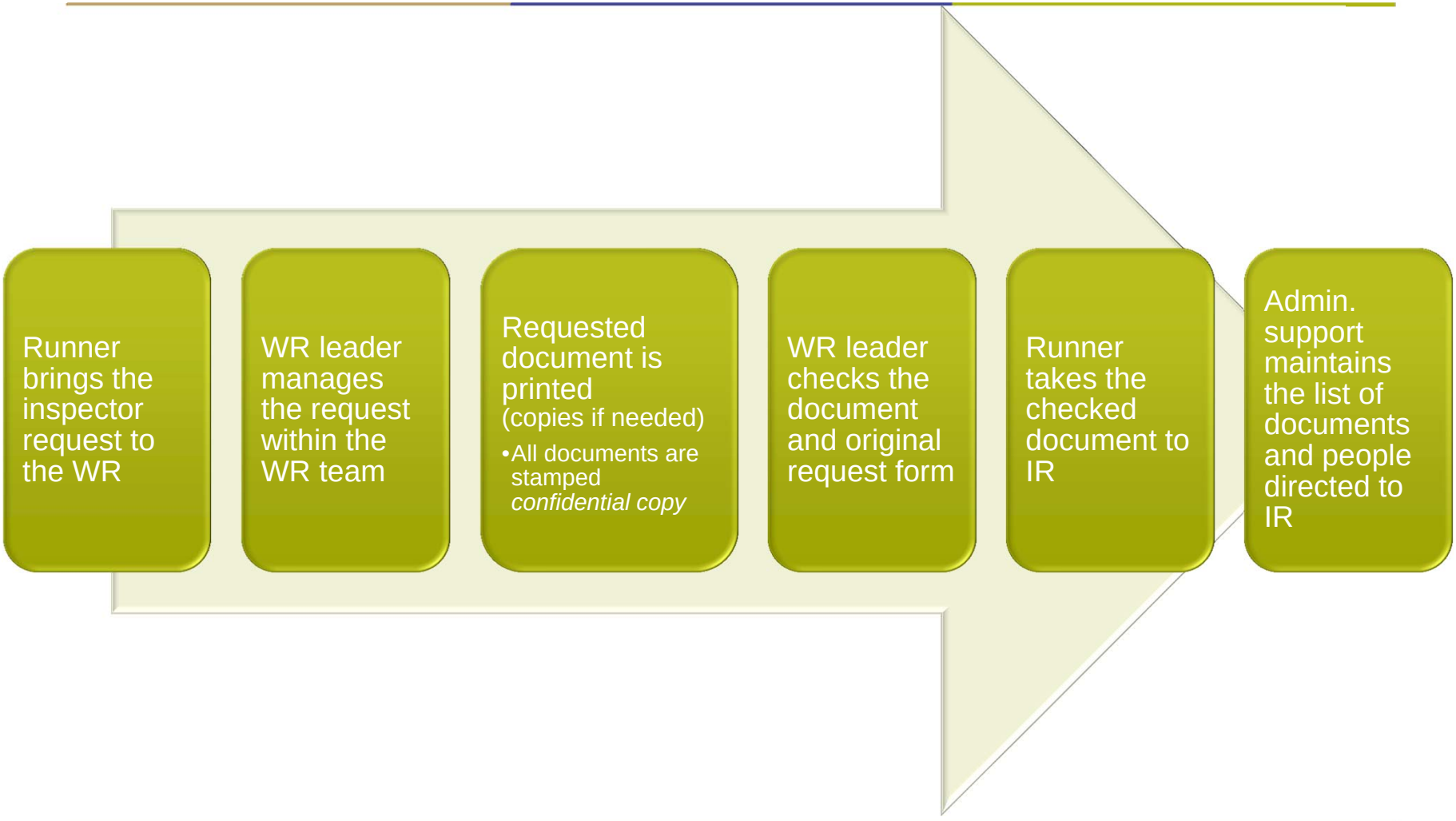
- **Obtains a copy of requested SOPs**
- **Organizes and manages the responses with impacted people**

Coach

- **Prior to talking with inspector**
- **Helps with stress**
- **Provides advice as to how to answer questions**

A war room can be set up if needed at the sponsor's to support site inspections

War room flow



Inspection progress

Opening meeting	• **Institutional presentations** • **R&D presentation (organizational charts)** • **Security / Safety instructions** • **Training (eTMF…)**
Debriefing / Closing meeting	• **Each day, inspectors will normally hold a debriefing meeting** • **On the last day, closing meeting** • Attendees selected with inspectors agreement • **Inspectors will share findings, remarks…**
Internal debriefing	• **Held every day after inspectors left** • **Open to anyone impacted by the inspection** • **Remind action plan for the following day** • **Anticipate inspectors requests**
Daily summaries	• **Written, gathered and circulated by QA** • **Based on notes taken during the inspection**

After inspection report reception

Inspection report

- As soon as received by clinical team, the report is shared with QA
  - If needed a translation in English may be requested
- The Clinical Team and QA:
  - prepare response letter to inspectors within agreed timelines
  - define the corrective and preventive actions: develop objective answers based on documented evidence
  - define timelines for CAPAs implementation
- The Clinical Team submits final response letter and CAPAs to QA before communication to inspectors
- The Clinical Team ensures that all CAPAs are implemented on due time and documented

The Clinical Team remains available until inspection closure

Pause 3

Preparation for inspections and audits

INSPECTIONS

Investigator site preparation

US FDA will normally contact the Sponsor first * but if you are contacted

(*for out of US inspections)

- Confirm the following with the Inspector
  - The full name and department along with full contact details of the person calling**.**
  - Ask (*politely*) why? (*Is it a routine purpose or directed inspection* ?)
  - Who will be coming? (*Record the name(s) of inspector(s*))
  - When?
  - How long?
  - Scope of the inspection (*which study or which studies*?)
  - Any specific requests to prepare in advance?
  - Can a Sponsor representative be allowed to attend?

REMINDER:

Please notify the Sponsor as soon as you are contacted by any Agency

Following an inspection announcement letter

Sponsor notification

- PI immediately informs the Sponsor of the inspection announcement
- PI provides a copy of the announcement letter
- Sponsor sets up an inspection support team

Former inspection verification

- Was the site already inspected?
  - PI checks inspection reports, findings and CAPAs
- Were others sites inspected by the same Agency?
  - Sponsor checks inspection reports, findings and CAPAs

Inspectors' expectations

- PI and sponsor work together on inspectors' requests
- PI asks for clarification if needed

How can an investigator site be inspection ready at anytime?

Conduct the trial in compliance with:	• protocol • ICH GCP • regulatory requirements
Produce and maintain source documents to permit evaluation of:	• the conduct of the trial • the quality of the data produced
Keep and maintain files:	• in an orderly and chronological manner • in designated cabinets with restricted access
Ensure that processes in place at the site are:	• logical • traceable • well documented

How to prepare the site facilities for an inspection?

Clean and tidy facilities	• Meeting rooms, offices, trial-related rooms… • Remove confidential files, personal belongings, post-it notes, personal screen savers…
Information on notice boards	• Do not display passwords, trial related issues, humorous posters…
Inspection room	• Large enough to accommodate inspectors and relevant site, CRO and Sponsor staff • Free of any documentation not requested by the inspectors • Telephone/internet access for inspectors
Tour of the facilities for the inspectors	• Organize the tour of the trial-related areas (reception desk, physical examination wards, blood sample and IP administration areas, waiting rooms…) • Never leave the inspector alone

Prior to Inspection

- Ensure that all affected departments are aware and inspection ready
  e.g. pharmacy, laboratory etc.
- Conduct mock inspection interviews with relevant staff members
  e.g. using typical questions from inspectors – see examples listed hereafter
- Ensure all necessary documents are readily available
  - ➢ Have a plan for showing the inspector any Electronic Medical Records and systems
    e.g. arrange for EMR access, if the system allows limited access to a particular study
    - If limited access is not possible, designated staff should always be with the Inspector to show these data
    - Never leave the Inspector alone with an unlocked computer system and ensure passwords are protected
- Prepare a list of all studies performed by the PI (see pages 13 of 45 of CPGM).
  a. Protocol number; b. Protocol title; c. Name of sponsor d. Study dates.

Note: if the Sponsor is allowed by the Agency to be present

➢ Have a separate room for preparing requests, discussions and for phoning out if needed

What are inspectors looking for? (1/9)

PI and Site Staff

- PI's oversight of the site (and satellite sites if applicable)
  - Adequate resources and facilities
  - Appropriate delegation of study related tasks
  - Regular and documented meetings with site staff
- PI and site staff have proper knowledge of the study
- PI keeps an up-to-date knowledge of the subjects' progress in the trial
- The study is completed as per protocol requirements
- The archiving process

List of site staff working on the study

- Study task delegation
- Signatures and initials
- Site specific organizational chart

What are inspectors looking for? (2/9)

Training / Qualifications of site staff

- The site staff is trained and informed on the trial specifics
- They are qualified by training and education for the tasks delegated to them

Site resources

- Site workload: number of ongoing clinical trials
- Staff workload is manageable to give adequate time to the study

Relationship with the sponsor

- Communications between PI and sponsor
  e-mails, monitoring visits and CAPAs follow-up
- Sponsor oversight of the trial
- Monitoring of the progress of the trial

What are inspectors looking for? (3/9)

Ethics committees' approvals and communications

- Approvals – conditional or final
- Institution Review Board / Ethics Committee is compliant with ICH E6
- Correspondences with PI
- Periodic updates by PI

Regulations and requirements

- Health Authorities communications

What are inspectors looking for? (4/9)

Source documents and source data

- All subjects medical records are present / available (paper and/or electronic)
- Source documents and source data are **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal, **A**ccurate and **C**omplete (ALCOAC principle)

Data collection

- Accuracy of data in CRFs / completeness with source documents
  Electronic Medical Charts: may request validation information (secured access, 21CFR part 11 compliant)
- Secure archiving of paper medical charts (storage facility) during and post trial
- Confidentiality / data privacy
- Data validation by the sponsor during monitoring visits (source data verification, corrections / queries)
- Data integrity throughout data collection and transfer phases

What are inspectors looking for? (5/9)

Subjects

- Informed consent / assent procedures (all original signed forms)
- Subjects' primary physician/pediatrician information
- Compensation / indemnity
- Compliance with protocol
- Source documentation management and completeness
- Adverse events reporting to sponsor, IRB/EC and HA according to local procedures
- Emergency procedures
- Compliance with randomization/blinding procedures

Safety reporting

- SAE reported within required timeframes
- Causality assessment done & documented
- Forwarding of safety reports to IRB/EC
- SAE subject follow-up through to recovery

What are inspectors looking for? (6/9)

Investigational Products (IP)

- **IP management on site**
  - Shipment documentation to the site
  - Dispensation
    - Room or location of IP preparation before administration, injection
  - Accountability
  - Returns, disposals / destructions
  - Implementation and maintenance of blinding procedures
- **IP storage area**
  - Cold chain management
    - Temperature records
    - Process in case of cold chain break
  - Restricted access to storage area
  - Dedicated space to quarantine study IP
- **Equipment**
  - Maintenance records for fridges, cold room…
  - Temperature monitoring device calibration

What are inspectors looking for? (7/9)

Blood samples

- **Blood samples management on site**
  - Blood samples collection
    - Documentation
    - Room for blood sample collection
  - Shipments to sponsor

- **Blood samples storage area**
  - Cold chain management
    - Temperature records
    - Process in case of cold chain break
  - Restricted access to storage area

- **Equipment**
  - Maintenance records for centrifuges, freezers…
  - Temperature monitoring device calibration

What are inspectors looking for ? (8/9)

Investigator Site File

- **CVs**
  - Site staff CVs up to date
  - Pediatric and emergency training to be covered

- **Training records and related documentation**
  - GCP training (documented on CVs, certificates, attendance logs…)
  - Study specific trainings (investigators meetings, eCRF…)
  - Applicable site/hospital procedures (subjects registration, local lab, IP destruction…)

- **Availability of up to date study documents** (including version and date)
  - Protocol, protocol signature
  - Investigator Brochure
  - Operating Guidelines – IPs, samples, cold chain management…
  - e-CRF Completion Guidelines…

What are inspectors looking for ? (9/9)

Quality Features of Documents

- Inspectors expect the following:
  - Documents record ‘quality’ data – accurate, reliable and complete
  - Documents are permanent
  - Documents are legible
  - Documents are version controlled
  - Documents are easy to photocopy

  Sites should NOT recreate or revise documents for an inspection

Typical questions from inspectors

Investigator / Sub-Investigator / Study Nurse / Coordinator Interview

- *How and by whom was the site contacted to initiate the study?*
- *What is the hospital specialization and structure?*
- *What training has been given for the study (i.e., protocol, ICH-GCP)?*
- *Do you have regular training on ICH-GCP?*
- *How many studies are you currently involved in?*
- *What has to be in place before you can start the study (i.e., IRB/EC approvals)?*
- *Who was involved in the conduct of this trial?*
- *What were your responsibilities and how were these delegated – is this documented?*
- *How were subjects recruited in the study?*
- *Who obtained consent from subjects?*

Typical questions from inspectors

Investigator / Sub-Investigator / Study Nurse / Coordinator Interview

- *Please explain the consent process. Do you have an SOP for this process?*
- *How do you check the subject eligibility?*
- *What about re-screens?*
- *Are you involved in any IRB/EC submission?*
- *Do you notify the subjects' General Practitioner/Primary Physician about the study? If so: How?*
- *Please explain the screening process.*
- *What is the role/involvement of the PI in a particular study?*
- *How do you as PI maintain oversight of the study?*
- *(How often) Do you discuss the study with the PI?*

Typical questions from inspectors

Investigator / Sub-Investigator / Study Nurse / Coordinator Interview

- *How do you communicate with the sponsor?*
- *How do you handle study medication?*
- *How do you manage temperature control for study medication?*
- *What do you do in case of a noted temperature excursion?*
- *Who is responsible for IPs accountability?*
- *Use of IVRS system (if applicable): What is it used for? Who is responsible for updates/has access?*
- *What is the SAE reporting procedure?*
- *How do you manage AEs?*
- *What is the process for SUSAR reporting? How were relevant safety updates communicated to the site?*
- *What is the process for unblinding subjects?*

Typical questions from inspectors

Investigator / Sub-Investigator / Study Nurse / Coordinator Interview

- *How do you record data?*
- *What does your source data comprise of, how is it organized and maintained?*
- *Who handles queries and sign off?*
- *What are the arrangements for long-term storage/archiving?*
- *What process do you have in place in case of an emergency?*
- *How are storage conditions monitored?*
- *How often do you see the monitor?*
- *Have there been any problems with the conduct of this study?*
- *How often do you speak to pharmacy / staff in charge of IPs?*
- *Did you have any issues with the central lab/eCRF/IVRS?*
- *Was the site audited in the past?*

Typical questions from inspectors

Additional questions if eCRF/eSource data (electronic records) are used

- *What training did you receive on eCRF use?*
- *Who enters which data into the system?*
- *How often does the PI review the data?*
- *How do you ensure that passwords are protected?*
- *How does the monitor review data (esp. e-source)?*
- *Is the eSource (electronic subject records) system validated?*
- *Does it maintain an audit trail? Can you access the audit trail?*
- *How was source data verification done by the monitor?*

Additional question for Research Nurse

- *What is process for taking blood samples? (Or other trial-specific examinations for which the nurse is responsible, e. g. X-ray, MRT, TB test)*

Typical questions from inspectors

Interview of Pharmacist / Site staff in charge of IPs

- *How are you trained on the trial and kept informed of changes during the trial?*
- *What are you checking for when you first receive the IPs?*
- *How do you confirm receipt?*
- *What training did you receive on IVRS/IRT use?*
- *Who enters which data into the system? Password protection?*
- *Please describe the IPs dispensing procedure.*
- *Was re-labeling performed, if so how?*
- *What is the process for unblinding?*
- *How do you document IPs accountability?*
- *What happens with the returns of IPs?*
- *How is IPs destruction handled?*
- *How are storage conditions monitored?*
- *What happens if a temperature excursion occurs?*

Preparation for inspections and audits

Investigator site preparation

Inspection progress

On the first day of inspection…

Inspectors arrival on site	• Reception desk checks inspectors identities • Escort the inspectors to the inspection room • Inspectors identification / credentials from the Agency will be presented (but do not take copy as it is illegal)
Opening meeting	• Brief presentation by PI • Introduction by inspectors • Scope of inspection • Sponsor representative may be present on site during the inspection if all parties agree
Hospitality and availability	• Provide basic hospitality during all inspection days (coffee, tea…) • PI and staff availability are critical during inspection, verify expectations and accommodate inspector's requests as much as possible.

All along the inspection

Be aware of data protection

- Unless specifically requested by the inspectors, copies of Source Documents given to inspectors should be anonymized (no personal identifiers)
- Copies of SDs requested by inspectors must be anonymized for those retained by Sponsor.

Inspection flow

- No original documents may be taken by the inspectors.
- Take minutes/notes on what is requested:
  - what questions are asked
  - how they were answered
  - what documentation was provided (if applicable),
  - make extra copies of documents requested
  - track if possible
  - store in a designated binder
- This will also help the sponsor's clinical team to support you in answering any requests/findings.
- Sponsor / CRO can support but will not be directly involved with inspectors unless specifically requested

All along the inspection

Debriefing meeting

- Each day, inspectors will normally hold a debriefing meeting
- Inspectors will share findings, remarks…
- The PI may clarify with the inspectors any observation raised that may be inaccurate or incorrect

Internal debriefing

- Every day, after the inspectors leave the site
- PI, site staff and sponsor will hold a debriefing meeting to:
  - review findings and remarks from the inspectors
  - prepare action plan for the following day

Daily summaries

- Written, gathered and circulated by Sponsor representative
- Based on notes taken during the inspection and from debriefing meeting

All along the inspection

Closing meeting

- The PI will clarify with the inspectors:
  - Any observation raised that may be inaccurate or incorrect
  - The inspection report availability
  - The timelines for responses to inspectors
- The FDA can provide a Form FDA 483 to the PI:
  - It is issued when the Inspectors observed any conditions that, in their judgment, may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts.
  - Request clarifications where needed and provide corrections at this time if something is inaccurate.

All along the inspection

After the Closing meeting

- The PI and/or Sponsor will prepare minutes of the closing meeting
- Sponsor and PI will analyze the inspectors' remarks and findings

- **If given a Form FDA 483**,
  - notify the Sponsor immediately (if absent)
  - work with the Sponsor to provide a response to then inspectors within 15 business days of the inspection
  - **Prompt response may alleviate or decrease the severity of a potential Warning Letter**.

- **If not issued a Form FDA 483**,
  - inform the Sponsor immediately (if absent)
  - your site still may receive later a communication from the FDA such as an Untitled Letter *(different from a Warning Letter as it does not include a statement warning that failure to promptly correct a violation may result in an enforcement action)*
  - provide the Sponsor with all documentation/reports issued from the inspectors

Pause 4

Preparation for inspections and audits

Inspection etiquette

Inspectors expectations

Cooperation

- **Site organization for the trial clearly described**
- **Clear, consistent and justified explanations**

Respect and honesty

- **Trustful behaviour**
- **Transparency**

Clear answers

- **Feel confident**
  - Gaps are identified and action plans are in place
  - Show your knowledge on the trial

Inspection Do's: General behaviour

Set-up your mobile phone on mute

Have your badge visible (if any)

Introduce yourself

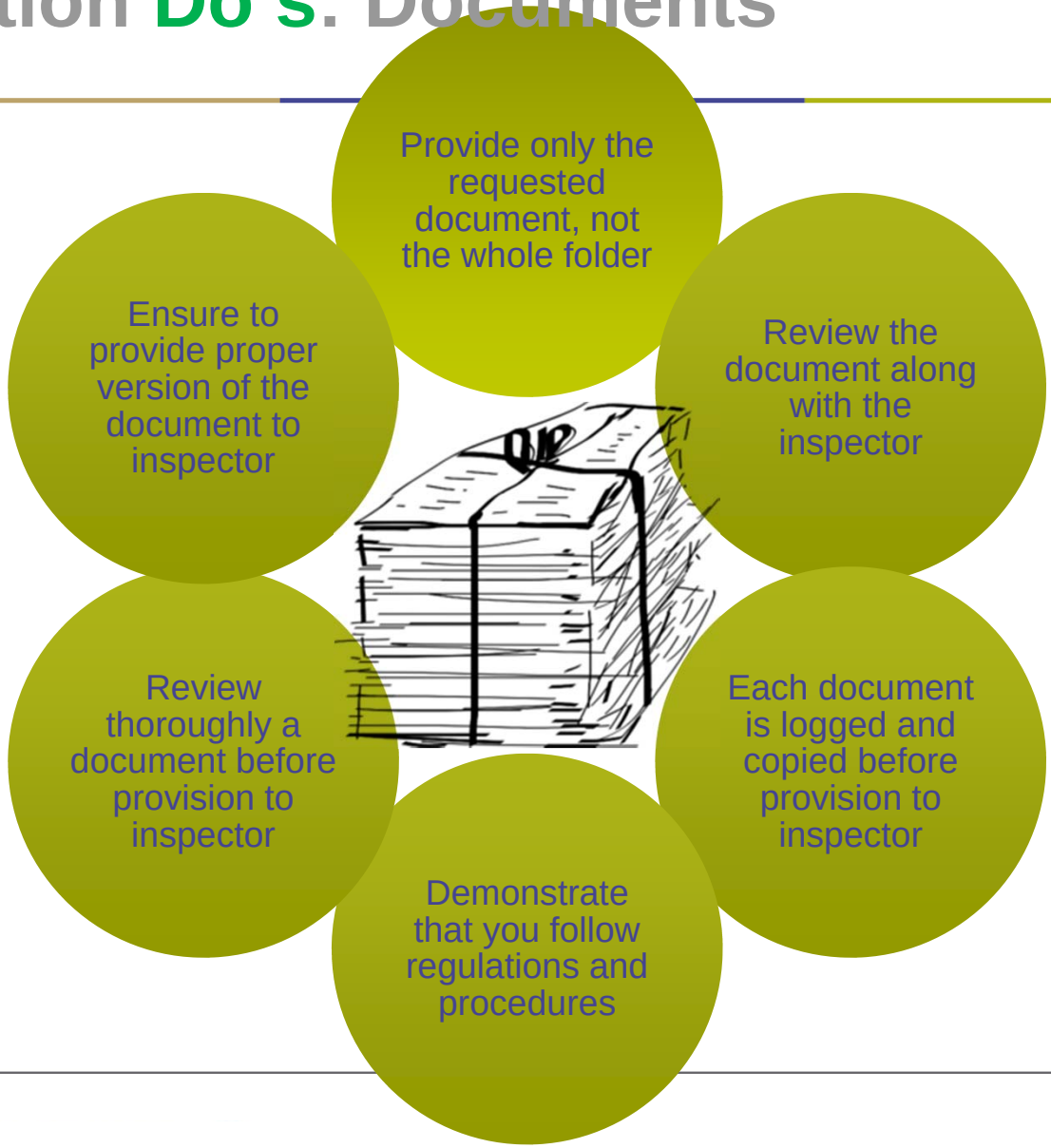
State your name, title and function clearly

Be careful to chats during breaks and in the corridors

Control your body language

Inspection Do's: Positive Behaviour

Inspection Do's: Documents



Inspection Do's: Answers

Provide information quickly and efficiently	• If you do not know the answer, just say so
Give concise and unequivocal explanation	• Answer "yes" or "no" when appropriate
Provide only information within the scope of the inspection	• Provide only requested information
Understand the meaning of the question prior to answering	• Ask for clarification if question is not understood
There is nothing wrong with silence	• Remain silent if inspector is silent
Show interest in comments and recommendations	• Portray your will to improve your knowledge

Inspection **Don’ts**

Panic	• Keep calm
Leave the inspector unaccompanied	• He might come across something you don’t want him to see
Refuse to collaborate	• You might give the impression that you have something to hide
Assume that the inspector is naïve, uninformed or inexperienced	• It will backfire on you
Let the inspector think there are exceptions	• He might think procedures are not followed properly
Questions the colleagues work, blame someone or make excuses	• You should be confident in yourself and your co-workers
Question the inspector findings	• Act as a professional

Inspection **Don’ts**

Answer if you don’t know	• Tell him someone else will answer his question
Answer questions in advance	• Let him come to the point
Give vague or incomplete answers	• That could lead the inspector to draw inaccurate conclusions
Guess at answers or use the words ‘I think’, ‘I assume’, ‘I guess’	• Remember, portray confidence!
Make conversations within blanks	• There is nothing wrong with silence
Prevent inspector from looking at a document	• That could lead the inspector to think something is wrong
Let the inspector find himself a document	• All documents provided to him must be tracked

Inspection **Don’ts**

Assume inspectors don’t understand your native language	• Keep remarks far from inspectors ears
Express an opinion and show the issues	• Let him draw his own conclusion
Point out errors identified during the session	• This is his job
Provide a document without recording it	• Documents have been lost this way
Comment on the quality of data reviewed	• It is his job to find what is wrong, our job is to make sure everything is fine
Let the inspector access a computer system under an unauthorized regular user ID	• No tracking would be possible in such occasion
Speak about future improvement plans	• Inspectors are interested in the current situation

Preparation for inspections and audits

AUDIT versus INSPECTION

Audit versus Inspection

AUDIT	INSPECTION
Independent Quality Audit is part of the **Quality System** of the **Sponsor**	**Official act** conducted by **Regulatory Authorities**
Auditors	**Inspectors**
Detection of **non-conformities** / Evaluation of the **Quality system**	Observation of **non-compliances with Regulations**
Audit reports • for Auditees & **Sponsor management** • Continuous improvement • Recommendations and action plans	**Official Inspection Report** Mandatory requirements: • Responses • Action plans
May result in **notification of misconduct** • Ethics Committees • Regulatory Authorities	Inspection Reports from Authorities may result in **legal actions**

Preparation for inspections and audits

Be ready anytime and anywhere !

To be ready for Audits and Inspections:

Ensure compliance with GCP and regulations during daily activities

Thank you !