

# Preparing investigator sites for inspections

Shelly Bustion  
Bliss Consulting Sàrl

# Reasons Behind Inspections (1/2)

There are **four reasons** for the Health Regulatory Authority to call an Inspection :

1

**Routine inspections:** inspections of the systems and procedures used to conduct clinical research in order to assure compliance with applicable laws and regulations.  
Organization is notified of routine inspections in advance.

2

**For cause inspections:** these are ad-hoc inspections that may be triggered as a result of suspected violations of legislation relating to the conduct of clinical trials.  
The organisation may or may not be notified of these inspections in advance.

# Reasons Behind Inspections (2/2)

3

**Committee for Medicinal Products for Human Use (CHMP)** requested inspections resulting from central marketing authorisation (MA) submissions: the CHMP can request GCP inspections in relation to marketing applications made using the EU centralised procedure. The European Medicines Agency (EMA) coordinates these inspections, which are conducted by inspectors from the EU Member States.

4

**Follow up** - to ensure that CAPAs have been implemented

# Notification of an inspection



- Starting date and expected duration - varying from day(s) to week(s)
- Name of inspectors (1-2 inspectors for FDA / European Agencies more)
- Reason for the inspection
- Requests for specific personnel or specific documents

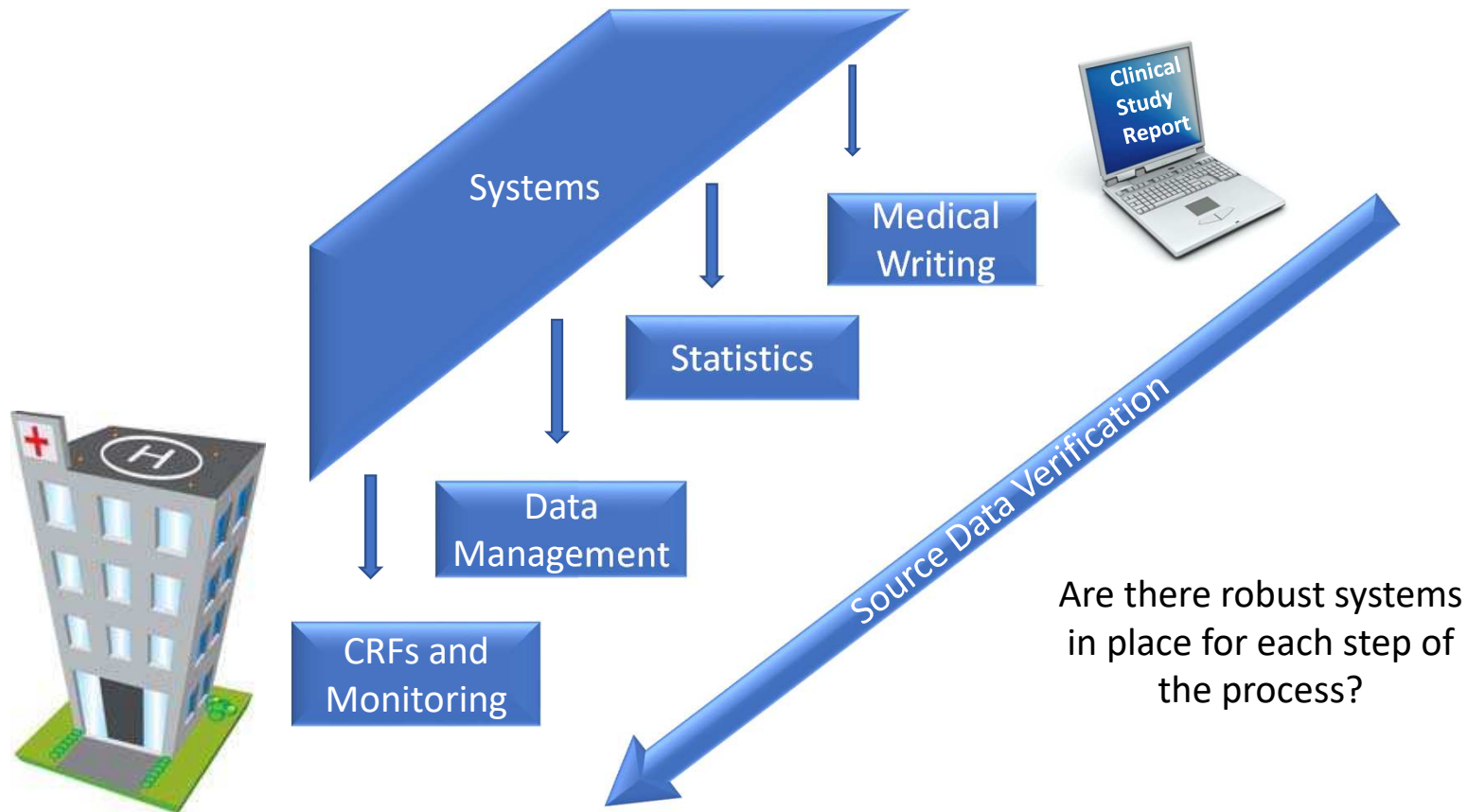
**Inspections might be unannounced (FDA)!**

# Inspection Objectives



- Verify compliance with applicable regulations and processes in place. Inspector(s) assess compliance with:
  - GCP guidelines
  - ICH guidelines
  - Local Regulations
  - Applicable Standard Operating Procedures (SOPs)
- Determine data integrity and validity of studies in support of pending marketing authorisation application
- Determine whether the rights and safety of human subjects of clinical research have been adequately protected

# What the Inspector is looking for ?



# What the Inspector is looking for during a Site Inspection (1/2)

- Has Informed Consent been properly obtained from each subject? Time given to subjects to read the Informed Consent Form (ICF)? Process thoroughly documented in subjects records?
- Have adverse events been properly handled? How has the Principal Investigator (PI) reported serious and unexpected adverse effects to the Ethics Committee (EC) and/or to Sponsor, as per local requirements?
- Does the PI retain control and oversight of the study conduct & has any authority been delegated? Is the PI able to state what changes were made with the implementation of each amendment?
- Site personnel are properly qualified and trained and proper documented delegation to qualified personnel

# What the Inspector is looking for during a Site Inspection (1/2)

- Has the EC reviewed & approved the protocol, & every change to the protocol (amendments)?
- Do enrolled subjects meet the protocol eligibility criteria ?
- Is sufficient documentation available at site to demonstrate conclusively that subjects existed & were alive & available to participate in the study?
- Do study reports accurately compare to raw (source) data?
- What level of drug accountability is there? How is/was the drug dispensed & returned & who controls/controlled these activities?



# Key stages in preparation



1. Prior to notification of inspection
2. After notification and before commencement
3. On “the Day”
4. Preparation for inspection reporting
5. Inspection responses
6. Inspection Do’s and Dont’s
7. After “its all over”

# 1. Prior to notification of inspection



- Begin today, if not yesterday!
- Make sure you are familiar with Good Clinical Practice (GCP) requirements
- Insure appropriate training of all site staff involved:
  - On Study specific requirements
  - Assess their past GCP and clinical trial experience
  - Ensure their knowledge of other relevant local regulatory requirements

# 1. Prior to notification of inspection



- Prepare the team for the inspection
- Maintain accurate information and up to date records, including Investigator Site File
- Prepare relevant departments involved in the study conduct
- Consider performing a Mock Inspection (by Sponsor/Quality Assurance)

# 1. Prior to notification of inspection



## Pre-Inspection Activities

- Review documentation and findings from previous inspections and audits
  - What findings were noted?
  - Was a response or action plan provided?
  - Have action items been implemented and documented?
  - Have problems re-occurred?

## Reminder:

- **A mix of technical skills and soft skills is needed**

*« Successful inspection depends primarily on good quality data but also on knowledgeable people that will present the data to health authorities »*

## 2. After notification and before commencement



### Preparation

- Conduct a prior review of any facility areas likely to be visited
- Note any errors that can be corrected in advance. This can include other departments which provide services to the study
- The most important thing about presenting to an inspector is to know where everything is

*You are not expected to know everything, but the inspector(s) will expect you to know where to find it.*

## 2. After notification and before commencement



### Pre-Inspection Logistics

- Determine who will be available to assist with the inspection and respond to questions
- Reserve an inspection meeting room that is private, large enough to accommodate the inspectors, but separate from the work area and documentation
- Ensure access to telephone for the inspectors
- Make power sources for laptop computers available
- Organize refreshments and food for the inspectors

## 2. After notification and before commencement

- Liaise with assigned inspector
- Make arrangements and agree an agenda
- Ensure all staff are aware of the scope of the inspection
- Identify which study/ies may be considered
- Supply further documents as requested



## 2. After notification and before commencement



- Sponsor visit of the investigational site
- Establish the scope of the inspection
  - Why it is happening?
  - What support will be provided or expected?
  - Who are the main contacts for the site and for the sponsor?
  - What is likely to occur
    - Number of inspectors, site staff and sponsor personnel
    - Agenda and timings
    - Possible outcomes
- Involve all staff who may be interviewed or contribute

## 2. After notification and before commencement

- Locate study files in all departments in-house and at the site
- Prepare site staff (by Sponsor or Contract Research Organization [CRO])
- Establish availability of staff, facilities and documentation
- Check location and availability of essential documents
- Prepare for meetings - locations, timings and roles

## 2. After notification and before commencement

### **Visit relevant locations**

- Pharmacy
- Laboratory
- Other service departments
- File storage

### **Look for and resolve problems**

- Organized tidy appearance
- Cleanliness and minor repairs
- Security

## 2. After notification and before commencement



### Carefully check the site files and documents

- All present
- Filed in correct order
- Readable and identifiable
- All required signatures present
- Complete logs
  - Temperature control
  - Investigational Medicinal Product (IMP)
  - Samples
  - Recruitment
  - Subject identity
  - Approved signatures
- Review Case Report Forms (CRFs)
  - All queries resolved
  - All corrections attributable
  - Users properly trained
  - Data entered after the user was trained
- Source documents
  - Available
  - Identifiable
  - Complete

**Follow the ALCOA guidelines**

## 3. On “the Day”

Site arranges to:

- Give the inspectors time to settle in
- Show them the facilities
- Tell them about your fire evacuation arrangements
- Provide
  - Appropriate refreshments and food
  - Sufficient quiet space
  - electricity points for laptops
  - Photocopy machine
  - Escort/assistance

## 3. On “the Day”

The usual pattern of an investigational site inspection

- Introductory meeting
- Tour of facilities and equipment review
- Interviews
- Documents review
- Exit meeting

### 3. On “the Day”

- The PI is encouraged to be present at introductory and exit meetings as a minimum
- The PI provides introductory background information about how the study was organised and conducted at their site
- If possible have a Sponsor Quality Assurance (QA) representative and Clinical Research associate (CRA) present.
- Take detailed notes of Questions & Answers (Q&As)
- Keep a list and copies of all documents supplied to the inspector
- Discuss with the inspectors who will attend the exit meeting

# 3. On “the Day”



## Discuss with the site staff

- How much should you say?
  - Be welcoming (remember first impressions - perception)
  - Stick to the point (answer only the question posed)
  - Bring out your best (be empathetic)
  - Refer when necessary
  - Don't argue (but seek clarification if you think they have misunderstood)
- Provide good quality background information



# Interview Techniques (1/3)



- To obtain additional volunteered information
- To validate or invalidate information already gathered
- To compare information
- To test knowledge or understanding
- To identify potential issues or concerns
- To assess honesty, integrity and credibility

# Interview Techniques (2/3)



- **Silence:** The first who speaks loses (volunteering information as we feel awkward in silence). Wait for the Inspector's next question patiently. Silence is ok, don't feel compelled to fill the "void" by talking.
- **Open-ended questions:** To get additional information. If you feel uncomfortable, request specificities on the question. More detailed question will get you to remain on point.
- **Fishing:** Try to ask for specific question and provide information only on the specific topic (e.g. question on use of a document/SOP) but only how you used it/applied it to the study.

Text inspired by Victoria Niven

# Interview Techniques (3/3)



- **Redundant confirming questions:** Stick to the same answer provided earlier during the interview and maintain a record of questions asked, responses and documents provided.
- **Hypothetical questions:** What would you do? How would you handle? Just refer to a process in place. No need to elaborate since this has not happened and is only a “what if” ...
- **Eye contact and body language:** Maintain eye contact and be aware of body language.

Text inspired by Victoria Niven

## 4. Preparation for inspection reporting

- Politely discuss any inspection finding or observation that is inaccurate or incorrect (do this before the inspector concludes inspection)
- Provide lists of names, titles and functions of those interviewed or involved
- Provide the addresses of relevant locations
- Establish who will receive the report and how any findings will be transmitted to the appropriate persons (PI, Sponsor, etc.)
- Explain that there may be requirements for action and timelines for responses and actions

# Most frequent findings



- Failure to follow the protocol
  - Eligibility, timings, missed procedures
- Inadequate study drug accountability / study drug issues
- PI's lack of involvement/oversight
  - Delegation and training
- Failure to maintain adequate source documents (SDs) /CRF/ SD inconsistencies (ALCOA Guidelines)

# Most frequent findings



- Inadequacies in obtaining informed consent and/or in performing protocol procedures
- Problems relating to reporting of serious adverse events
- Monitoring
- Essential documents
- Facilities and equipment
- Laboratory tests

## 5. Inspection Responses

- Reply as required within the timelines
- Stick to the issue raised
- Remember to issue a Corrective and Preventive Action Plan (CAPA)
- Make sure you do what you promise

## 6. Inspection DOs and DON'Ts



### **DO**

#### *Pre-inspection activities:*

- Notify assigned personnel and management
- Make sure you receive an agenda of the inspection with scope and duration
- Inform any site staff likely to be involved in the inspection, such as the pharmacist, lab staff, etc. and ensure they are fully briefed about the inspection. Identify and appoint staff members who can take an active part in the inspection due to their experience in the trial
- Retrieve all documentation pertaining to the study and keep available
- Select and book a suitable meeting room for the duration of the inspection
- Appoint an assistant to help with document retrieval, photocopying and taking minutes during the inspection



## 6. Inspection DOs and DON'Ts



### DO

#### *During the inspection:*

- Request credentials (identification) of the inspector(s) upon arrival and escort inspector(s) to the inspection room
- At the initial meeting, confirm how long the inspection will last
- Ensure a scribe is present during all interviews to provide a comprehensive record of the inspection and a record of all documents requested and provided
- Determine with the inspectors which records they need for review and answer only the questions asked. **Do not provide them with anything additional to their request and do not volunteer information.** Ensure all your staff is informed of the above.
- If photocopies are requested, ensure patient names are removed where relevant. Duplicate all copies (to keep an inspection trail at site and for the Sponsor) and stamp them “Confidential” prior to giving them to an inspector

# 6. Inspection DOs and DON'Ts



## **DO**

*During the inspection:*

- Offer your assistance or that of appointed staff members to guide the inspectors through the records and help them locate documents. If this is not required, come and ask the inspectors periodically if they do not require assistance.
- Always accompany the inspectors if they ask to visit a specific area such as a lab or the pharmacy
- During discussions, ask “Shall we move on?” rather than “Any further questions?”
- Cooperate, be professional and courteous. Be confident at all times
- Be honest and straightforward in answering questions

## 6. Inspection DOs and DON'Ts



### DO

#### *During the inspection:*

- If you don't fully understand a question or a request, take time to ensure you have clarified it prior to answering
- Remember, an inspection is not a memory test!
- Provide information as quickly and efficiently as possible
- Request daily briefings/wrap-up from the inspector (if more than one day)
- An exit interview must be held with the inspectors at the close of the inspection. **Never let an inspection end without having requested the opportunity to discuss the inspection findings with the inspectors. You must take this unique chance to clarify potential misunderstandings.**

## 6. Inspection DOs and DON'Ts



### **DON'T**

- Don't leave the inspector unescorted to examine files
- Don't try to guess a reply
- Don't give vague or incomplete answers which could lead to inaccurate conclusions

# Always Remember:



Surviving an inspection does not happen by Magic!

- If it is not documented, it did NOT happen!
- The Principal Investigator is directly responsible for addressing the action items resulting from a site inspection, in close collaboration with the Sponsor (or CRO/delegate). The Sponsor (or CRO/delegate) will provide assistance to elaborate the response to the authorities when required.

## 7. After its all over!

- Inspectors may visit again
- They will refer back to previous inspection reports and agreed actions
- Use your record of the previous inspection

**Subsequent inspection is more likely if previous responses have not been satisfactory!**

# Even without a follow-up inspection



- Seize this opportunity to review processes
- Use the enthusiasm and motivation to achieve prompt, efficient and relevant actions/improvements
- Review your standard operating procedures (SOPs) as required

# SUMMARY



“Be prepared”:

- Inspectors place a heavy emphasis on their own preparation
- Develop a firm commitment to the principles of GCP throughout the organisation
- Conduct ethically and scientifically sound research
- Have up-to-date standard operating procedures (SOPs)
- Train your staff
- Learn from and enjoy the experience... if you can!



# BACK-UP

# ALCOA Guidelines



## Attributable

It should be clear who documented the data.

## Legible

Readable and signatures identifiable.

## Contemporaneous

The information should be documented in the correct time frame along with the flow of events.

## Original

Earliest record. Changes and/or corrections should not obscure prior entries.

## Accurate

eCRF should be a valid representation of the source data.