GCP Inspection Readiness for Sponsor/CROs

Why would you deliberately put your team through the stressful situation of a mock inspection?

Are you confident that your quality system can withstand the scrutiny of a regulatory inspection? We work every day with the quality systems we developed but it is surprising how an outsider may view your quality system and can be embarrassing that the obvious is missing or non-compliant. Any audit or inspection can be a stressful experience and the learning curve can be very steep, but very beneficial.

Performing or, better still, asking a consultant to perform a mock inspection can be invaluable. If the whole process is conducted as close to reality as possible, staff will know what to expect, will see first-hand why certain documents and processes are so important and will experience a formal interview about their roles and tasks.

The team knows exactly what a SOP means and how to complete all the steps, but how will they react when faced with a formal interview to explain this (I've seen the most confident employee become completely tongue tied). When a process is very familiar it is often difficult to articulate this in a concise, logical way and steps are missed. How will an outsider who doesn't know the nuances of the company terminology read a pre-inspection dossier and SOPs. Do these documents accurately convey the actual process to an outsider/inspector?

Inspectors often talk about reconstructing the events of the trial – does the documentation tell the story of the trial and, most importantly, the complete story in a logical manner? Or are crucial dates, documents or communications missing? ICH-E6 requires the documents to individually and collectively permit evaluation of the conduct of a trial, the quality of the data produced and to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and with all applicable regulatory requirements.

Objectives of a Mock GCP Inspection for Sponsors/CROs

This toolkit focuses on the conduct of routine GCP inspections of a sponsor or CRO. Although there are some differences in the way in which different regulatory authorities conduct inspections, the objective of any regulatory inspection is fundamentally the same. That is to verify that the rights, safety and well-being of trial subjects are protected and that the clinical trial data are credible, hence the overall approach to conducting an inspection should be similar.

PRIOR TO THE INSPECTION

Pre-inspection Dossier (if appropriate)

Inspection Team	Sponsor/CRO
■ Although not required by all regulatory authorities, the use of a dossier or similar document as a tool for gathering information from the sponsor/CRO is recommended and will help to determine the scope of the inspection and the time required for conduct ■ Review completed dossier or similar document, scrutinise the information provided against the requirements specified and seek clarification as necessary. IT information is one area where misinterpretation can ensue, particularly regarding who houses what data and where ■ Provide feedback on the dossier completion.	■ Ensure you have the latest template or understand the requirements ■ Take care to read all instructions ■ Ask the appropriate staff to prepare a draft or provide the requested documents ■ Ensure enough detail is included to allow the process, etc. to be understood and ensure only required information is provided ■ Review to ensure the requirements have been meet and cover the correct time-point i.e. the correct version of an SOP is provided ■ Take special care if the previously submitted dossier is used as a starting point because the template and requirements do change.

Preparation for the Inspection

■ Determine the scope and time frame based on the size of the company, number of trials and the trial activities undertaken. If the sponsor outsources an activity(s) to a CRO/subcontractor then the scope of inspection may be limited to review of sponsor oversight of the outsourced activities ■ Liaise with the client to determine the most appropriate staff for interview. It is preferable to select individuals from each area of operation that actually perform the inspected activities on a daily basis rather than senior/management staff but the client may suggest those they feel would benefit most from interview practice ■ Prepare interview questions. Use different questioning styles e.g. open-ended questions ■ Use a risk-based approach to select two or three clinical trials for review, e.g. occurrence of a serious breach, first in human trial or high risk IMP. If mimicking an FDA inspection this will typically cover trials related to a particular submission and pivotal trials may be selected for review. Other selection criteria for consideration include: – Trial status e.g. completed trial so that end of trial activities such as site close-out activities, database lock procedures and generation of the clinical study report can be reviewed – Number of sites involved – If management of trials has been outsourced to different CROs then it is recommended that trials managed by different CROs are selected ■ Draft the inspection plan using e.g. the information from the dossier and send to the client for input. The plan should detail names/titles of inspectors, dates of inspection, areas of operation to be reviewed including approximate times of interviews, names of interviewees, documentation that should be available and detail of the selected trials. Factors to consider when drafting the inspection plan include: – Language barriers and the possible need for translations – Whether all interviews can be done face-to-face or if teleconference/ videoconference will be necessary (time zone differences should be taken into consideration) ■ Where applicable, refer to a prior inspection report to review previous findings. Gather intelligence on inspection trends via discussion forums (e.g. MHRA's, RQA's, MHRA Inspectorate Blog), inspection metrics reports, FDA warning letters, redacted MHRA inspection reports.	■ Notify all staff and request that all annual leave during the inspection is notified to QA – to allow them to relay this to the inspectors, if needed ■ Request that no further annual leave is booked to ensure as many staff as possible are available to be able to request the most knowledgeable person to answer any questions ■ Request all staff to treat this as though it was a real inspection – to gain the greatest benefits from the exercise ■ While waiting to find out which studies will be reviewed: – Check all training records – Identify any areas of weakness/possible inspection findings, analyse and handle appropriately – Ensure all SOPs have been reviewed according to the SOP on managing SOPs – Ensure all filing is up to date especially the eTMFs (this should already be up to date - refer to UK SI 2006 / 1928 Reg 31A) – Ensure the office is tidy, if not already. This often brings to light documents that should have been filed/archived! ■ Plan logistics – Main inspection room and one interview room per inspector preferably away from the offices – Lunches (remember to ask if the inspectors have any food restrictions), tea, coffee and water. Ensure this is basic and could not be perceived as bribery ■ Perform training for all staff on the process and expectations ■ Plan back room: who, where and process ■ When studies for the inspection have been announced and interviewee identified: – Circulate agenda with rooms and note-takers identified – Perform more in-depth training for staff who will/may be interviewed, including practice interviews – Review all eTMFs that are subject of the inspection – QA review all training records for all interviewees – Ensure any training required for accessing electronic document management systems is prepared and reviewed – Source and setup laptops/computers for the inspectors to use to access any electronic document management systems – Ensure security/reception know what will happen and how they should behave, including checking the identity of the inspectors. It is always good to explain why it is important to the company.

DURING THE INSPECTION

Inspection Team

- Present at the facility under inspection – ID check
- Facilitate opening meeting – this should include introductions, confirmation of the agenda and the scope and objectives of the inspection, brief company overview presentation by sponsor/CRO

> Ensure the overview presentation does not overrun as this can eat up valuable time.
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> Use the presentation to gather information and clarify areas of ambiguity, particularly in relation to organisational structure, reporting lines.

> Bear in mind the MHRA's revision of critical findings in 2014 to include '...the TMF is not readily available or accessible...'

> Review SOPs prior to interviews if possible to allow pertinent questions to be asked and procedural awareness and compliance verified in the most effective way.

- Undertake any necessary training e.g. in the use of an eTMF
- Review SOPs and other procedural documents to determine if they are fit for purpose and compliant with regulatory requirements
- Interview staff – to determine if what they say they do matches with the requirements of their SOPs and meets with regulatory requirements
  - Start each interview with some general questions relating to training and awareness of regulations, followed by more specific process-related questions or focused questions generated from documentation review
  - Interviews should not be intentionally intimidating and interviewees are not expected to be able to recite SOPs verbatim
  - Factor in 'off the record' time, allowing discussion between inspectors and client on any areas of concern/ambiguity, etc.
- Review a sample of staff training records – to determine if they are adequately qualified through education and experience and appropriately trained to perform their delegated tasks
- Sample review of trial documentation – to verify if procedures are being conducted as per the SOPs and other procedural and trial-specific documentation and in compliance with regulatory requirements
- Document requests – request documents as appropriate, e.g. during interviews, to support the information provided and to verify compliance with e.g. procedural documents. If mimicking an MHRA-style inspection, log documents requested on a document request form
- Review facilities, e.g. server rooms, document storage, general security – to ensure they are fit for purpose
- Review CAPA completion for a selection of findings identified during prior inspections of the organisation
- Closing meeting – feedback observations and confirm the reporting procedures. Highlight that the grading of observations is provisional. Issue an FDA form 483 if mimicking an FDA-style inspection. As the mock-inspection is essentially a training activity, feedback any areas for improvement and discuss if additional training may be beneficial e.g. interview training.

Sponsor/CRO

- Welcome inspection team and check identification
- Ensure fire evacuation procedures are notified to the inspection team
- Inform the inspection team of the location of the toilets, this may require the provision of a security pass
- Present training for any electronic document management systems and ensure user IDs and passwords are provided clearly in writing
- Take notes of all interviews and questions asked – collate these
- Keep a record of all documents requested by the inspection team (this is normally achieved by copying all requests twice and maintaining one copy, in the back room)

> If not an MHRA mock inspection, suggest a document log is utilised to ensure all requests are fulfilled.

- At the end of each day, prepare a brief report for the management team
- Meet as a management team to discuss issues, if appropriate.

AFTER THE INSPECTION

Inspection Team

- Issue the inspection report in a format similar to that used by the regulatory authority which the mock inspection is mimicking and provide necessary guidance as applicable
- Ensure responses include effective corrective and preventive action plans with timescales for both
- Seek clarification on responses where necessary
- Once responses have been accepted, issue a GCP inspection statement, if applicable (dependent on regulatory authority procedures).

Sponsor/CRO

- Ensure, you understand all findings
- Determine the root cause (this does not need to be formally documented)
- Prepare response and corrective and preventive actions, as appropriate. Include person responsible and date by which it will be completed

Ensure all responses are reviewed and are S.M.A.R.T.

Specific
Measurable
Achievable
Realistic
Timely

Once responses have been accepted, start working, ensuring that an evidence file is created.

Karen Martin
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REFERENCES

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