A sponsor's guide to preparing for GCP inspections for clinical trials

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Abstract
The scope of a GCP inspection at a sponsor site can include review of the Trial Master File, sponsor oversight evidence, other management documents such as CAPA reports and training records, electronic systems and validation evidence.

This article discusses the routine maintenance activities and preparative actions beforehand, including training of staff and organisation of the inspection environment. Early planning and ongoing inspection readiness are key to a successful outcome.

Since the EU Clinical Trials Directive was published in 2001,[1] there has been a mandate for European competent authorities to conduct good clinical practice (GCP) inspections before, during and after a clinical trial. During that time, the majority of all but the newest European sponsors and clinical research organisations (CROs) will have undergone at least one GCP inspection. In the US, the FDA has conducted GCP inspections under the Bioresearch Monitoring Program (BIMO) since the 1970s. But however familiar organisations might become with the process, the prospect of a forthcoming inspection remains a daunting one. Preparation is the key to ensuring a smooth and edifying inspection experience.

Although inspectors do have the right of entry, it is more usual for inspections to be announced in advance. The initial notification may be accompanied by a request for information in the form of a dossier, which will then be used to determine the scope of the inspection.

Regardless of the timing of the notification, however, there is a general expectation that documents, systems and facilities should be maintained in a state of inspection readiness at all times. This is achieved by conducting research activities in a timely way. With the advent of electronic document management systems, inspectors are taking an increasing interest in metadata, particularly regarding the generation and filing of documents in relation to the events that they record. Thus, inspectors reviewing an electronic Trial Master File (eTMF) will take a close look at the dates on which documents have been filed, and tend to take a dim view if dates appear to peak shortly before the scheduled inspection.

Inspection readiness – when to begin?

The best inspection preparation occurs where a culture of readiness is embedded within an organisation. This can be generated by:

- Ensuring that all employees know that their activities might be subjected to external scrutiny by including inspection awareness within their induction programme
- Producing a standard operating procedure (SOP) to cover hosting regulatory inspection and/or external audit. The SOP should include the identification of a primary point of contact for the inspection team, themes for preparation, and processes before, during and after the inspection
- Maintaining an active quality assurance (QA) programme of systems and trial audits, so that employees are familiar with the experience of their activities undergoing external review
- Conducting periodic mock inspections, including review of documents and facilities, and practice interviews.

Trial Master File (TMF)

The primary focus of many GCP inspections is documentation associated with selected clinical trials. National regulatory authorities conducting routine risk based inspections will request information in advance relating to the sponsor's trial programme, and from this will select a number of trials for inclusion in the inspection. Both ongoing and completed trials may be included. In addition, it is worth bearing in mind that inspectors reserve the right to extend the scope of the inspection.

When the inspection has been requested in association with a marketing authorisation application (MAA), then the inspection will focus on trials associated with the investigational product (IP) which is the subject of the MAA.

The TMF is the repository of essential documents, that is, documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. The TMF can be paper based or electronic. A skeleton of the content of the TMF is set out, among other places, in the International Council for Harmonisation (ICH) GCP guideline.[2] However, this is widely regarded as a starting point rather than a definitive list. Therefore additional items may be included as required to demonstrate adherence to process, eg, checklists and plans.

The inspectors will generally expect to be able to review the TMF with minimal assistance from the sponsor, particularly if the trial has already concluded. This means providing paper files for review, or ensuring that the inspectors have independent access to the eTMF.[3] A short period of training (no more than one hour) is deemed acceptable to acquaint inspectors with the electronic filing system. While the trial is ongoing and the TMF is a work in progress, the inspectors may accept input from the clinical trial team to explain the current status of the trial and documents.

It follows therefore that time should be spent in advance of the inspection in checking that the TMF is complete or up to date. As much as possible, all the essential documents should be at the same location. If there are logistical or organisational reasons preventing this, for example, if the same Investigator's Brochure (IB) applies to several studies and is therefore held in a single central location, then that location should be clearly cross-referenced in the TMF. Bear in mind that if that central location changes at some point, then the TMF should be updated.

Responsibility for the majority of the TMF generally falls to the Clinical Operations Group. However, it is not unusual for several departments

within an organisation to take responsibility for different sections of the TMF. Regulatory, pharmacovigilance and/or chemistry, manufacturing, and controls (CMC) departments may have good reasons for looking after their own file sections. However, a common inspection finding is that there is a lack of understanding as to which documents, particularly those managed by other departments, should be included in the TMF. Process evidence is often missing, for example:

- Statistics: In addition to a statistical analysis plan (SAP) and statistics outputs for the clinical study reports, inspectors might expect to see documented decisions regarding the exclusion of trial subjects from analysis populations
- Regulatory: Inspectors will expect to see regulatory correspondence as well as approval letters.
- Contracts: These may be held separately by a legal group, but they often contain key information about the division of responsibilities within a trial. While the financial arrangements may not be of direct interest to the inspectors, a redacted copy of contracts with financial information removed can be supplied for filing in the TMF.

Therefore it is very helpful to have a TMF plan which identifies locations and responsibilities. In the run-up to the inspection one group should take responsibility for the coordination of the TMF and ensuring that all items can be accessed.

When the Good Clinical Practice Directive was published by the EU in 2005, the following statement was included in Article 17:[4] "Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities." Part of general inspection preparation should therefore include checking archive retrieval systems to ensure that documents can be provided in case of short notice requests.

Inspection and sponsor oversight of externally managed trials

Where a TMF is being managed by a CRO on a sponsor's behalf, this should be disclosed in advance to the inspectors if the trial is selected for inspection. If a paper TMF is being stored at a different location, the inspectors will either request for it to be transferred to the sponsor for the inspection, or make arrangements to view it in situ.

Regardless of the location of the TMF, the sponsor will be expected to demonstrate oversight of the trial while it is in progress. Oversight evidence can include contracts, sponsor sign-off of key trial documents (protocol/plans), meeting minutes, correspondence and documentation of key trial decisions. These would be held in a sponsor's management file or similar in the sponsor's office.

The latest version of the ICH GCP guideline requires that "the sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s)."[2] Evidence for this oversight might include showing that the contractor's own vendor selection processes have been reviewed by the sponsor, identification of each organisation contributing to the trial, and any accreditations or other evidence of suitability.

Preparation of other documents

Other documents which the inspectors may request to see in order to demonstrate overall adherence to GCP and compliance with regulatory requirements include:

- Quality management system (QMS) documents, including policy documents, SOPs and working practices. Inspectors commonly request these documents in advance, so be prepared to discuss and demonstrate review, approval and dissemination processes.
- Audit programme information, including as applicable, the annual audit schedule and audit conduct evidence. In the first instance it may not be necessary to disclose all audit reports to the inspectors, as this is believed to compromise their objectivity. However, it is useful to have audit certificates available, and subject to specific request be prepared to provide audit plans or reports.
- Corrective action preventive action (CAPA) reports. If there has been a previous GCP inspection, prepare a CAPA file which contains the previous report, the agreed CAPAs and for each one, evidence of implementation and follow-up. If the CAPA was not implemented, prepare the rationale for this and evidence of any alternative actions. In any case, be ready to discuss and demonstrate the process for the management of CAPAs arising from internal systems audits or external audits from client and partners.
- Serious breach or misconduct reports. For trials involving UK subjects, serious breaches of the protocol or GCP must be reported to the MHRA within seven days. This requirement will extend to other European countries once the European Clinical Trial Regulation[5] has been fully implemented. All sponsors should be able to demonstrate the process in place for identifying and escalating reported episodes of research misconduct.
- Training records for employees and contractors, including CVs, GCP training evidence, SOP training evidence and any relevant internal or external training. Involve each staff member with checking that their own records are up to date, even when these are held centrally. It is important to include evidence of line manager oversight, for example annual review or appraisal sign-offs. Be aware that training may be documented in separate locations, including the TMF for trial specific training, within an electronic learning management system for SOP training, or within the human resources department. All should be available for inspection. Ideally training procedures should be captured within an SOP; if not, a staff member should be prepared to discuss the process with the inspectors.

Electronic systems

Inspectors will expect access to electronic versions of essential documents relating to the selected trials, if this is the format used for their management. As well as the TMF,[3] this may include the electronic Case Report Form (eCRF).

Where electronic management or analysis systems are used (eg, clinical trial management systems, clinical database, interactive response technology for randomisation or treatment assignment), as well as reviewing their outputs, inspectors may request computerised systems validation (CSV) evidence. If the software has been developed in house then the CSV evidence should be readily available, both for the product itself and for any trial specific functions which have been developed on the platform. For off-the-shelf software or software which has been developed by a vendor, the sponsor should still have access to the CSV package, and have retained evidence of user acceptance testing (UAT) and authorisation for use within the sponsor organisation.

One of the key requirements of electronic systems within GCP is that they include audit trail functionality. This may be included in the inspection, for example, in the case of an eTMF, inspectors may review the associated metadata, so that they can see when documents have been added to the eTMF and if any changes have been made subsequently.

Mock inspection

Let's assume that all of your documents and systems are inspection ready on an ongoing basis! Running a mock inspection is a great way to test the systems under realistic conditions, thus identifying and correcting weaknesses ahead of the real event. It also helps staff, particularly those

who may not have been through an inspection before, to know what to expect and how they should conduct themselves during an inspection. Practice in advance reduces anxiety. Mock inspections work best if the assigned inspector is either external or usually based in a different part of the organisation.

The scope of the mock inspection should include selection of two or three trials which are known to be at higher risk, where for example there have been a high number of adverse events or deviations or a first-in-human trial. If the mock inspection is designed to mimic an FDA or EMA inspection, then the focus may be on trials associated with a particular regulatory submission.

Once a date has been agreed, review all documents and systems to ensure everything is up to date. Notify all staff and prepare the environment. Specifically ensure that any items relating to other projects are cleared from sight, desks are clear and computer screens are closed down when unattended.

Inspection roles should also be assigned, including:

- Inspection host to welcome the inspection team, shows them where to sign in, escorts them while on site and makes introductions
- Scribe to record meetings and interviews
- Subject experts prepared to discuss assigned aspects of selected trials or company systems
- Runners to call people into meetings and forward document requests.

Prepare a room for the use of the inspection team, and if possible have a second office available as an operations room. Whether or not a second room is available, ensure that staff discussions are conducted well away from the inspection room.

Practice interviews should be included in the mock inspection, to prepare staff for the kind of questions which they might be asked. Questions can cover an individual's education and training, and their role in the activity under review. Trial-specific questions might include matters relating to adverse events, trial deviations and issue escalation. Interviews may also be conducted with a group rather than an individual. In this case interviewees should try to avoid contradicting and speaking over one another.

Once the mock inspection has concluded, a subsequent debrief can be held to consolidate its educational value. It will also allow participants an opportunity to express any difficulties they experienced and resolve any disagreements or misconceptions which may have arisen. Deviations or findings may have been identified which require further action, including CAPAs and impact assessment.

Conclusion

Maintaining a state of inspection readiness requires vigilance, but pays off in staff knowledge and confidence, enhanced quality, and operational systems in a state of continuous improvement.

References

1. EU Commission Directive 2001/20/EC, 1 May 2001.
2. International Conference on Harmonization Guideline for Good Clinical Practice E6, November 2016, adopted by CHMP, 15 December 2016, issued as EMA/CHMP/ICH/135/1995.
3. EMA Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials EMA/15975/2016, 31 March 2017.
4. EU Commission Directive 2005/28/EC, 8 April 2005.
5. Regulation (EU) number 536/2014 on clinical trials for medicinal products for human use, 16 April 2014.