HOW TO PREPARE FOR A GCP INSPECTION

What is the purpose of the inspection?

GCP inspectors have responsibility for assessment of the processes which determine the ultimate safety, quality and efficacy of the drug under investigation. In addition, they have an equal duty to ensure that the ethics and the safety of the potential subjects have been assessed and carefully monitored.

A typical GCP inspection involves a multitude of factors, many of which are somewhat outside the direct control of the Sponsor. Investigators' priorities are divided between their research and their other clinical responsibilities. Human subjects are not contractually bound to comply with protocols. Studies' activities are rarely performed in a controlled environment. These factors may, and frequently do, have an effect on the inspector's findings and make diverse and sometimes unexpected demands on those involved in the conduct of clinical research and the process of GCP inspection.

Who can Inspect?

- Sponsor (in accordance with ICH GCP 5.1.1 & 5.1.2.)
- Domestic Competent/Drug Regulatory Authority
- Foreign Regulatory Authorities (eg US FDA)
- Contract Research Organisation (CRO) (ICH GCP 5.2.1) on behalf of the Sponsor
- Ethics Committees (Local and National)
- Hospital Research & Development Departments

Why Choose to Audit you?

- level & nature of research activity
- number of clinical trials being conducted
- recruitment figures unusually high
- previous inspection history & findings
- unusually low numbers of serious adverse events and adverse events
- whistleblower / misconduct / fraud
- result of sponsor's central monitoring statistical testing

Internationally, competent authorities (those government agencies charged with the responsibility of reviewing GCP compliance) vary in their approach to inspection.

Preparation for inspection should consider the following stages:-

1. Prior to notification of inspection
2. After notification and before commencement
3. During the conduct of the inspection
4. Inspection reporting
5. Inspection responses
6. After "it's all over"

1. Prior to notification of inspection

Preparation for regulatory inspection should begin long before the reality of such an event and should be considered at the point you decided to become involved in Clinical Trials. The whole philosophy of the conduct of research should reflect the principles of ICH-GCP. Evidence of commitment to these principles is the purpose of regulatory inspection. This cannot be achieved in a few weeks hurried activity after an inspection is announced, but should be built into every trial related procedure.

Be familiar with GCP requirements

In addition to the Sponsor everyone involved in the conduct of clinical trials, including all Study Sites, should comply with the principles of ICH-GCP Section 2 which relate to the ethical conduct and scientific basis of studies undertaken, to the handling and presentation of data, the manufacture, handling, storage and use of investigational products and the implementation of systems to assure the quality of all aspects of clinical research.

Recruit and train appropriately

More specifically, sponsor, investigational and contract research organisation (CRO) (if relevant) clinical research staff should be qualified by education, training and experience to perform their tasks. (ICH-GCP 2.8) This has implications for staff recruitment and ongoing training and for selection and training of investigators.

Establish GCP compliant Standard Operating Procedures (SOPs)

Ensure SOPs are up-to-date and truly reflect current practice. Train staff in the required procedures and document this training.

Include a SOP on dealing with regulators

Although GCP is not specific about the range of SOPs that should be prepared, it is advisable to include a procedure on the management of the various types of regulatory contacts which may occur. This should include regulatory inspection in each of the relevant Good Practices. As for all SOPs, this procedure should be prepared and/or agreed by those most involved in the activities and agreed by senior management. Copies should be readily available to staff, who should be aware of its contents and trained in the procedures described.

Learn what to expect during an inspection

Preparation for inspection should be related to a knowledge of what usually happens in a regulatory inspection. Attendance at conferences, discussion with colleagues and a review of the literature are all fruitful areas for supplying this insight. It is worth remembering that inspection is really only a formal audit and, as in GCP (5.1.1), requires the sponsor to implement and maintain quality assurance.

2. After notification and before commencement

The period after notification of the proposed inspection and before the actual arrival of the inspectors is clearly the most critical phase of the preparation period. Typically this period will be anything from two weeks to two months long. However on some occasions inspectors may arrive unexpectedly and no notification will occur. When this happens the SOP on handling regulatory inspections has a particularly important role, as no additional preparation will be possible.

Assuming that some notice has been received of the proposed inspection, a number of activities may be undertaken and some of these will be requested or required by the inspectors themselves.

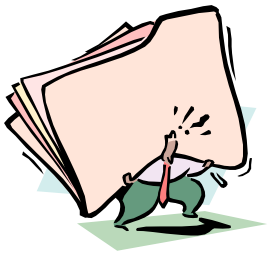
Consider appointing an Inspection Co-ordination Team

The team is of most value when it is multi-disciplinary and can liaise between the relevant departments and sections before, during and after the inspection. The team may take responsibility for co-ordinating all the stages of preparation for the inspection and may also deal with logistical matters.

Provide documents to the Inspectors

The protocol

If a specific study is to be the focus of the inspection, inspectors will typically ask for a copy of the protocol and consent documentation to be forwarded to them to allow them to prepare for the inspection. It is important to ensure that all amendments to the protocol are submitted to the inspectors. It is common for incorrect versions of documentation or incomplete documents to be submitted.



The Investigator Brochure

The inspectors may also require a copy of the investigational brochure and again it is worth considering whether earlier versions were applicable during the period of the conduct of the study and should, therefore, be submitted in addition to the current version.

Consent documents

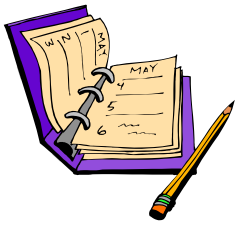
With regard to consent documentation, the inspectors will expect to see the patient information sheet and the blank consent form to be signed by the investigator and the

patient. If a generic consent form has been prepared as part of the protocol this will be submitted and site-specific versions should also be provided if these are in use. Check that the versions submitted are those approved by the Ethics Committees and further that they are those actually in use at the investigational sites.

Other documents

Other items may also be requested by inspectors in advance of the inspection, or alternatively, they may be required to be made available at the time of the inspection itself. In either case, it is useful to set up an Inspector's Folder containing all such information. A duplicate folder is usually prepared so that you have a complete record of the information submitted to the inspectors. The folders can be supplemented during the course of the inspection and the duplicate folder can subsequently be related to the inspection report and can be invaluable in preparing for subsequent inspections.

Make arrangements



In addition to the provision of the information in the Inspector's Folder, inspectors will also wish to have a number of other matters clarified for them in preparation for the inspection. In particular, an agenda and set of appointments should be agreed.

3. During the Inspection

The tasks can be divided into two sections: Firstly, preparation for a review of sponsor quality systems; secondly, preparation for the study-specific aspects of the inspection. Select what is relevant based on the type of inspection anticipated.

Hints:

- Avoid Major system change pre-inspection
- Ensure staff familiarisation with SOPs, policies, support departments and their locations
- Ensure version control & completeness of documentation
- Have evidence for testing out of hours / emergency procedures
- Recognise areas of weakness & identify corrective action
- Be honest

Sponsor Quality Systems

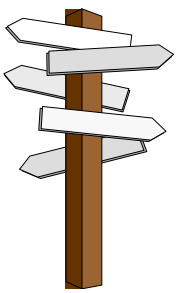
Prepare your SOPs and ensure that various functions and departments are prepared to host the inspectors if requested. Ensure that the necessary documentation is available and all staff members are aware of what may be required of them. Personnel should be prepared for a review of their training records, curriculum vitae and job descriptions. Inspectors may not confine their attention to the more senior members of staff, so even the most junior should be prepared.

In preparing staff for potential interview, it is important to discuss the degree of openness to be shown to inspectors. It is also important to reassure staff that inspections are not usually a test of memory. Members of staff may have reference documents available and should not be afraid to refer to them when questioned by inspectors. Inspectors will, however, expect members of staff to be familiar with the documentation and to find relevant information quickly.

In addition to statements made by members of staff during interview inspectors will also expect to see documentary evidence of the activities described. Please bear in mind the famous quote "if it isn't documented, it's rumour!"

Inspectors might wish to visit specific functional areas and will observe at the same time as interviewing and reviewing documentation. It is sensible to conduct a prior review of the areas likely to be visited to note any obvious issues which can be corrected in advance.

Study Specific



One of the primary foci of the study specific inspection will be documentation. Therefore, preparation should involve a review of the study files for the presence of the essential documents detailed in Section 8 of the ICH GCP Guidelines, and for the general condition of the

files. This review should include not only the study masterfile within your clinical department, but also any study-specific files within other departments such as data management, statistics and pharmacovigilance.

Preparation of personnel for the study specific aspects of the inspection should reflect the comments in the previous section and should include staff at the investigational site. Many investigational staff will be completely unfamiliar with the process of inspection and may not have even experienced a quality audit. They will be apprehensive and will require reassurance and preparation.

Initially, it is important to describe to the investigator and his/her staff what is the purpose of the inspection. Then the likely inspection procedure should be outlined, who will be present with the inspector and what documentation and areas the inspector is likely to wish to see. You should establish the availability of relevant staff and of support facilities such as photocopying, domestic arrangements for drinks, lunch etc, a base for the inspectors to work in, power sources for laptops and location of toilets and local transport amenities. The inspection team should determine which sponsor staff will be available to accompany the inspectors at the investigational sites.

It is particularly important that a member of the sponsor staff review the investigator file immediately prior to the inspection. This should ensure that nothing has been altered or removed since the last check, usually by the monitor. Investigators may have required a copy of a CV, for example. They have temporarily removed the copy from the study masterfile and forgotten to replace it.

It is important to establish who will be required for both the initial interview and the closing or exit interviews. The location and timings should be agreed as far as possible in advance but all staff should be aware they should maintain flexibility to accommodate changes in the planned inspection schedule. The Inspection Co-ordination Team should determine who will represent them and take records of the conduct of meetings with the inspectors.

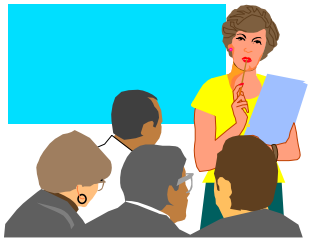
The Inspection – what to expect:

- ❑ Arrival
- ❑ Inspector Lead Opening Meeting
  - Introductions
  - Review of plan
  - Update on significant changes
  - Expectations
- ❑ Staff Interviews
  - Expectations:
    - o Are the correct people involved in the trial?
    - o Are they able to describe their roles and responsibilities?
  - Who can be interviewed? Basically anyone with a role in the trial set-up, approval and conduct.
    - o clinician
    - o research nurse
    - o data manager/data assistant
    - o statistician, pharmacist
    - o QA manager
    - o medical records personnel
    - o R&D manager
    - o IT staff
    - o ethics administrator
    - o project manager
    - o support departmental staff

4. Reporting the Inspection

Prior to the reporting phase of the inspection the Inspection Co-ordination Team within the Sponsor Company should discuss with the inspectors who will be the recipients of the final report.

To aid accurate reporting and to save time inspectors should be provided with lists of names, titles and functions of all those interviewed or otherwise involved in the inspection, and the full addresses of all relevant locations.



It is useful to establish the form of the report, the manner of reporting and how requirements for action will be expressed within the report. Inspectors should also give guidance about the time-lines for responses and actions and the type of responses and/or evidence of action required.

5. Inspection Responses

Many companies are surprised by the amount of effort, which is required in the inspection follow-up period. When the inspectors have completed the final exit interview and left the final inspection site a natural sigh of relief is given, and there is a tendency to wish to relax.

However positive an inspection has been it is likely that some response to the inspection report will be required. This response should be regarded very seriously and will require considerable time and effort by conscientious company staff.

Those required to prepare responses should be briefed in the requirements of the inspectors with regard to the format of responses, an action plan should be prepared and agreed with management and staff should bear in mind that responses should be submitted to inspectors within the required time lines.

On occasions it will prove difficult to comply with time requirements of inspectors and where this occurs the difficulties should be discussed with inspectors as soon as the company is aware of them. Inspectors will vary in their flexibility in handling such issues.

The internal Inspection Co-ordination Team should be prepared to make a full record of the conduct of the inspection, the responses submitted and time lines agreed with inspectors. Either they or the quality assurance function should be allocated responsibility for ensuring that actions agreed are actually carried out.

Categories of Findings

- Observations
- Recommendations
- MAJOR
- CRITICAL

Consequences for CRITICAL Findings

- Suspension or Termination of Research
- Infringement Notices - inform ethics, sponsor, etc.
- Criminal Offences - contravening regulations - providing false or misleading information
- Penalties - Fine /Imprisonment

6. After it's all over

It is important to remember that after the inspectors have departed and the report has been finalised this is not the end. Inspectors do not cease to exist and may very well visit again. When they do that they will naturally refer back to previous inspection reports and agreed actions, and will be looking for evidence that these actions have been carried out and that problems and issues identified previously do not continue to recur. For this reason if you are notified of a subsequent inspection, the full record contained in the inspection file of the previous inspection will prove invaluable in your preparation for this new inspection.

Subsequent inspection is particularly likely if responses have not been considered to be satisfactory to a previous inspection.

However, fear of subsequent inspections should not be the primary driver in the follow-up to an inspection. The existence of the multi-disciplinary Inspection Co-ordination Team and the heightened awareness of staff and management in all functional areas of GCP principles should be seized as an opportunity for a review of the whole clinical research process. Enthusiasm and motivation should be high providing this review is prompt, efficient and relevant.

At the very least, as a result of the inspection experience it is sensible to review the SOP on handling regulatory inspection to determine whether in the future different of better procedures should be adopted.

SUMMARY

The motto “be prepared” is very relevant to regulatory inspections. Inspectors themselves place emphasis on their own preparation so ensure you do the same. However, with a firm commitment to the principles of Good Clinical Practice stemming from sponsor and Principal Investigators and running right down to the most junior members, staff should have little to fear from the visit of the regulators. Ethically and scientifically sound clinical practice should be taking place and ICH-GCP compliant up-to-date SOPs will already be in place. Staff will be trained and should be sufficiently adaptable to cope with regulatory inspection at short notice.

Although inspectors vary in their approaches, you may well find the inspection experience a valuable one and a useful learning experience.