

GCP Inspection priorities based on the experience of the MHRA

(Sensible Inspections)

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Motivation for GCP inspections



- To promote the safety and welfare of trial subjects
- To promote the integrity of results reported from trials.

Example cases will be presented to demonstrate the need for inspections in the UK.

Legal basis for inspections of IMP trials in Europe



EU Directive 2005 / 28

Article 25:

Ensure effective verification of compliance with
Good Clinical Practice

Article 26:

...examining both the study management procedures and the conditions under which clinical trials are planned, performed, monitored and recorded.....

How do we choose who to inspect



Options:

- Inspect everything – not feasible
- Only inspect in response to crises – reactive not proactive
- Something in between – Risk based inspections*
(Risk factors include nature of IMP, nature of subjects...)

* Compliance risk rather than clinical risk

Risk basis for GCP inspections

- **Prioritising surveillance inspections.**
Involves examining the organisation's procedures together with a sample of investigator sites.
- **Inspecting reported Serious Breaches**
UK legal requirement for sponsors to report –
inspection focus on elements of serious non-compliance
- **Referrals**
Request of regulatory authorities –
specific trials, or investigators, often focused on
pivotal data.

Typical numbers of Non-Commercial inspections, per year

Around 20 to 25 organisations (~ ¼ of annual total)

Leading to inspection of around 60 to 80 non-commercial trial investigator sites – in order to assess the application of organisation's systems for compliance.

This is a small proportion of the several thousand such sites involved in trials at any time.

Aim: by raising compliance standards of these organisations, the influence of inspections, on compliance, should be far wider than on just those trial sites inspected.

Typical inspection of non-commercial investigator site (part of systems inspection).

Typically ½ day per. 'site', with main activities:-

Introductory discussion with the trial team
(Investigator if available – usually notified in advance).

Review of trial files and source records

Tour of facility (if appropriate)

Discussion of any outstanding compliance issues

Site specific, inspection closing meeting

Prioritising what to look at

1 Directive 2005/28, article 16:

TMF shall be the basis for... audit..... and inspection...

2. On the basis of experience:

- IMP,
- Approvals,
- Protocol compliance (safety & efficacy)
- Safety reporting
- Consent (procedures and results).

Beginning to look closer at data and data management.

where serious findings tend to arise

IMP: Is it what it was intended to be?

Reporting Serious Adverse reactions:

No process, or process not applied.

No review for new safety signals (added value!)

Compliance with the protocol:

Delegation issues, PI supervision

Approval of trials:

Before initiation, before significant amendments

Examples of serious findings (1) – non-compliance with the protocol

Both ‘arms of a trial use highly toxic IMP. Patients on one arm accidentally prescribed and dosed for other arm of treatment. Cumulative medication produced high level of toxicity, one patient died because of this.

Lack of QC for prescribing, dispensing and dosing stages

Patients on HIV trial should have received IMP on 10 occasions. Because of a mistake in a planning (EXCEL) spreadsheet, 10/15 patients were dosed 11 times.

Lack of QC (against protocol) of planning tool.

Nurse organised IMP prescriptions. Did not check key lab. Results, for which the protocol required dose reduction. Patients continued to receive drug at levels which the protocol considered dangerous.

Inadequate training and lack of supervision by a trial physician.

Examples of serious findings (2) : IMP

Investigator used IMP sent by academic friend working in the USA. On inspection, no documentation available (even from USA) to show what the IMP actually was. (N.B. *Pre-CTA*).

Investigator had a local (retail) pharmacist import 'Licensed' IMP from USA. Turns out to have been manufactured by another retail pharmacy (In USA). No evidence that the IMP was of acceptable quality.

Examples of serious findings (3) : IMP (contd.)

- Cream used on neonates
 - 1) Manufacturer stated this should not be done - risk of sepsis.
 - 2) Cream re-packaged in pharmacy – no records of procedure.
 - 3) Cream did not contain preservative.
 - 4) Expiry date was exceeded before trial started.

- Manufacture in hospital pharmacy (No MAIMP)

Hospital pharmacy (No MAIMP licence) received IMP as powder. They produce a suspension of the powder and give the suspension to patients. No evidence that bioavailability was preserved in this new pharmaceutical form, or that suspension was homogeneous.

Example of serious findings (4): safety reporting

A University CRU, ran a multicentre trial (UK).

Draft publication of results had been presented.

Used results to obtain approval for a second, similar, trial.

Sold the data to a pharmaceutical company.

Inspection found many unreported SAEs,
some of which were SUSARS.

If known, the SUSARs would have stopped the trial.

Also, high ineligibility & poor data reliability

Summary of sensible inspections

Focus on systems of the sponsor

Sample a small proportion of trials (investigator sites) to assess application of sponsor's systems.

Minimal time required from PIs (Unless serious problem).

Focus on higher (compliance) risk areas / activities.

Critical findings: ~ half of non-commercial organisations inspected.

Sponsors are required to agree to corrective and preventative actions (CAPA).

Any Questions

