17 July 2013
EMA/INS/GCP/167386/2012
Good Clinical Practice Inspectors Working Group (GCP IWG)

Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for “routine” and/or “for cause” inspections, their investigation and scope of such inspections

Adopted by GCP IWG	12 June 2013
Adopted by CHMP	17 June 2013

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1. Introduction

There is a clear need to verify the GCP compliance of clinical trials included in applications to the centralised procedure, either as part of new applications, as extensions to existing authorisations for approved products, or as clinical information provided as part of post marketing obligations.

The EMA relies for the scientific review of centralised applications for marketing authorisations for medicinal products on the expertise located in the Member States. Inspections are conducted by Member States' inspectorates on behalf of the European Union. These inspections, which are co-ordinated by the EMA if they pertain to centralised applications, evaluate compliance with GCP and provide assurance to the CHMP with regard to the reliability and the quality of the data submitted.

In principle, all clinical trials that are part of a marketing application dossier could merit closer scrutiny e.g. by an inspection. However, this is not feasible and not always necessary. A GCP inspection is a time and resource consuming process and therefore a request for an inspection should be considered when triggers are identified and alternative method cannot provide the necessary assurance, or when unresolved issues remain at the end of the evaluation process. In order to monitor GCP compliance and provide on-going assurance, some applications are selected for routine inspections, however the applications, clinical trials and sites should be selected based on a set of factors to ensure that a range of different situations are covered.

Triggers may be detected at various phases of applications and assessments. They may be derived from the application dossier prior to the start of the evaluation (validation phase) and can also be used as predefined factors for the request of "routine" inspections, or they may follow from the assessment process itself leading to the request of "for cause" inspections.

The impact of the various triggers is clearly different and should be evaluated in the light of the entire application. In cases where multiple triggers are present, it may be helpful to discuss these items already internally and with inspectors to clarify whether and how these can be evaluated during a GCP inspection.

This document provides a non-exhaustive overview of the potential pre-defined factors that can be used for the selection of marketing authorisation applications (MAAs) to be part of a programme of routine inspections and non-exhaustive overview of potential triggers that can be detected at the different stages of the assessment process and that can help the assessor to decide on the need for "for cause" inspections and be used to prepare an inspection .

This document does not cover triggers specific for inspection of bioequivalence trials as this is the subject of a separate document also available on the EMA website.

2. Routine inspections

Routine GCP inspections are inspections carried out as a routine surveillance of GCP compliance, in the absence of a specific trigger or concern. These routine inspections should have a random element in that not all applications would necessarily give rise to a GCP inspection. In order to ensure that a range of different situations are covered and that the limited inspection resources are used to good effect, the following factors should be taken into account for the selection of MAAs, trials and sites for routine inspections:

- Selection of MAAs:
  - Quality of the dossier:
    - missing documents (e.g. lack of GCP Statements, lack of audit certificates, lack of information on the monitoring process etc.);
    - inconsistencies;
    - previous history of problems with the quality of the dossiers from this applicant.
  - Product type (e.g. recombinant product, monoclonal antibody, cell therapy, gene therapy, new chemical entities, blood product, orphan product, other).
  - Applicant/Sponsor/CRO (to which major/relevant parts of trial conduct have been delegated):
    - Size (big/medium/small enterprises);
    - First application from the applicant;
    - type of sponsor (commercial/academic);
    - inspection history (never inspected/long time lapse since last inspection /inspection with negative outcome) ;
    - The applicant is not the sponsor of the trial(s) ;
    - business related issues (bankruptcy, change of ownership, mergers, other organisational changes).
  - Scope of the clinical data (single pivotal trial, small number of patients, high contribution of a few number of investigators, retrospective data collection, case studies, bibliographic, standard clinical package, BE/BA study).
  - Therapeutic area/indication (e.g. complicated trial protocol, design, etc.).
  - Type of endpoint (soft/hard).
  - Target population (paediatric, other vulnerable, patients critically ill, emergency, all types).
  - Others:
    - countries in which the trial has been conducted (EU/EEA vs third countries/emerging economies);
    - old trial(s) in the application (for example pre-date ICH GCP Guideline, or predate the Directive 2001/20/EC)
    - availability of negative inspection outcome information from third country authorities (e.g. US FDA/others as applicable).
- Selection of trials: pivotal trials will be usually the ones selected for this type of inspection. In case more than one pivotal trial is involved consideration should be given to:
  - size of the trial (number of sites and patients);
  - complex trial organisation (involvement of high number of CROs/providers, sub-contractors, countries);
  - complex trial design.

- Selection of sites:
  - recruitment rate (high/medium/low);
  - sites previously not inspected by EU and/or third country inspectorates with which confidentiality agreements are in place in the area of inspections (e.g. US FDA) in order to improve the inspection coverage;
  - previous inspection history;
  - third country location, in particular from emerging regions;
  - selection of diverse geographical locations of the sites to be inspected;
  - sites for which concerns are raised in the CSR with respect to the reliability, validity or representability of the reported trial data.

In the context of the centralised procedure, the identification and selection of applications for routine inspection takes place just after the GCP validation phase and the proposal comes from the Clinical and Non-Clinical Compliance section, balancing the above factors with the nature of the applications in order to make the best use of the inspection resource available. The proposal is circulated internally and to the Rapporteurs and inspectors concerned for their final agreement on whether or not the proposal is acceptable or other candidates should be considered.

The Clinical and non Clinical Compliance section at EMA, after considering the information collected by the Validation Center, should ensure that a diverse range of applications, trials and sites are covered by the programme of routine GCP inspections based on all the above factors (see Annex 1 for an overview of the most commonly used selection criteria for routine GCP inspections). The applications selected for routine inspections will then be inspected in accordance to the inspection procedures available from the EMA web site.

3. For cause inspections

These are triggered inspections, which are requested by assessors because there is a concern about deviation from GCP in relation to the overall trial conduct or to the conduct at a particular site.

There is an overlap with some of the factors outlined in section 2 and used for the selection of routine inspections (e.g. inspections history, single pivotal trial etc.) since some of these concerns may also be observed by the assessors from a preliminary scrutiny of the dossier, without the trial data being directly implicated. Others may be identified during the evaluation phase when a more advanced scrutiny of the dossier has been performed and for this reason, the triggers presented in this section are organised taking into consideration some of the headings of the CPMP/ICH/137/95 Note for Guidance on Structure and Content of Clinical Study reports.

It should be noted that although triggers may be identified, an inspection may not always be immediately necessary and alternative mechanisms of investigation, which can involve discussion with inspectors or leading to questions to the applicant, may be more appropriate.

3.1. Ethics

- Lack of information about review by an Ethics committee for all or some clinical trial documents (e.g. protocol, subject information & informed consent, recruitment procedures) and for trial sites.

- No description about the ethical conduct of the study (e.g. inclusion of vulnerable patients, high incidence of illiteracy in the study population, requirement for witness etc.) and of problems encountered, if any.
- Apparent inadequacy of informed consent process or information provided to trial subjects.

3.2. Investigators and study administrative structure

- Complex administrative structure (e.g. involvement of high number of CROs/providers, sub-contractor etc.).
- Previous history of negative inspections for one or more of the parties involved.
- Ability of the parties involved to undertake the amount of work generated by the study (e.g. based on information from the principal investigator CV or if the determination of endpoints would have required to use central facilities, high number of patients in a particular site etc.).

3.3. Investigational plan

- Study design issues (e.g. complexity of the trial design, inadequate justification of the use of placebo and/or choice of active comparator etc.).
- Major changes to the protocol during the study (e.g. change in primary endpoints or in statistical methods or in inclusion/exclusion criteria)/many protocol amendments.
- Treatment issues:
  - Identity and characteristics of the IMP and treatments are unclear:
    - inconsistency between the protocol and the study report concerning the dosage forms, packaging, labelling, conditions for storage, dose, dosage schedule and duration;
    - specific stability susceptibility of the IMP with inadequate storage or shipping conditions;
    - preparation by pharmaceutical and/or clinical staff before administration;
    - alterations of the product during the study;
    - complex titration or dose calculation.
  - Assigning patients to treatment groups:
    - out of sequence;
    - imbalance between treatment groups;
    - insufficient information on randomisation (allocation) procedures.
  - Blinding:
    - lack of and/or inappropriate procedures to ensure blinding;
    - Inadequate measures to prevent unblinding (e.g. resulting from manufacturing processes dealing to distinguishable IMPs, from laboratory data/adverse reactions/lack of efficacy, or from unblinded people involved in the study, of from members of a data monitoring committee or when an interim analysis is provided etc.);

- Concomitant medication concerns (e.g. use of forbidden concomitant medication, concerns regarding interaction with concomitant medications/direct effects on the study endpoints etc.).
- Treatment compliance concerns (e.g. complexity of medication regimens, side effects, differences between sites etc.).
- Quality Assurance issues i.e. Information which indicates significant problems with trial conduct, GCP-compliance.

3.4. Study patients

- Disposition of patients:
  - Unusual/unexplained differences in the number of patients:
    - between the planned sample size and screened or randomised or followed up patients;
    - per treatment arm;
    - per study phase;
    - with respect to the type and prevalence of disease and characteristics of the site.
  - Unusual/unexplained differences between trial sites:
    - unusual high recruitment, drop out rate and/or follow up period;
    - sites with a burst of fast recruitment following a long period of inactivity;
    - sites involved late during the course of the study in order to boost the recruitment;
    - different rates of attrition of patients numbers when compared the proportion of screened to randomised patients at baseline between sites and the proportion of lost of follow up during the trial;
  - Differences between countries: unusual high recruitment and drop out rate.
  - Distribution and/or characteristics of subjects different from generally observed demographics and other patient characteristics for the disease or location.
- Protocol deviations: none/many/unexplained (e.g. in the eligibility criteria, study visit windows, prohibited medication etc.).

3.5. Efficacy and safety evaluation criteria and data

- Efficacy and safety variables:
  - Unclear or unexplained differences in the definition of the study variables between the protocol and the clinical study report.
  - Measurement of the efficacy or safety variables:
    - novel method or new analytical procedure;
    - need for specific equipment;
    - need for specific training of personnel;
    - suitability of the methods used for measurement;

        - Lack of/poor documentation of non-standard efficacy or safety measurements;
        - Lack of [adequate] provisions in the protocol for the efficacy and/or safety measurements (e.g. regarding clinical samples, no provisions concerning sampling, tube identification, assay conditions etc.).
    - Changes in facilities carrying out critical measurements.
    - Evaluation of clinical outcomes : if anyone other than the investigator was responsible for evaluation of clinical outcomes (e.g. the sponsor, external reviewers or an external committee), the following points of the data flow process should be considered:
        - appropriate instructions/training to the investigators for collecting and reporting efficacy parameters;
        - identification and independence of the external reviewers/committee;
        - procedures for training, review, evaluation and documentation of outcomes, including means of maintaining blinding.
- Statistical methods:
    - Change in statistical methods/endpoints during/after the study, in particular changes made prior to breaking the blind and/or unscheduled statistical analysis.
    - Patient(s) data excluded from analysis without reason(s) or with reasons that raise concerns, in particular when the results are favourable to the test product or when the decision(s) to exclude data might have been made following unblinding of the data.
- Implausibility/inconsistency of clinical data provided:
    - Conflicting results as compared to known literature data or other trial results etc.).
    - Data with unusual trend or abnormal degrees of variation or very little deviations (i.e. low or high variability of efficacy parameters that would be expected to have much higher or lower natural variability; unexpectedly low levels of (serious) adverse events reports or concomitant medication etc.).
    - Data which appears to be abnormally in favour of the test product compared with other investigators or other studies.
    - Inconsistent, inaccurate or incomplete data recording and reporting:
        - inadequate CRF design (e.g. protocol amendments not captured in the CRF);
        - lack of relevant data listings;
        - inconsistencies between patient data listings and reported data in the body text of the clinical trial report;
        - high number of missing values;
        - drop outs that does not meet the reviewer's expectation for the active substance or the type of measurement.

Annex 1

Overview of commonly used selection criteria for routine GCP inspections

Selection of MAA	Product type	Recombinant/ Monoclonal antibody
		Cell therapy/ Gene therapy
		New chemical entities
		Blood product
		Orphan product
		Other
	Applicant/Sponsor/CRO	Size (big, medium, low)
		First application from the applicant
		Type of sponsor
		Inspection history
	Scope of the clinical data	Single pivotal trial
		Small number of patients
		High contribution of a few number of Investigators
	Therapeutic area/indication	
	Target population	Paediatric
		Other vulnerable
		Patients critically ill
		Emergency
		All types
	Others	Third countries/emerging economies, EU/EEA EU/EEA
		Availability of negative inspection outcome information from third country authorities
Selection of (pivotal) trials	Size of the trial (sites and patient numbers)	
	Complex trial design	

Selection of sites	Recruitment rate (high, medium, low)
	Previous inspection history/ no previous inspection
	Location (third countries/emerging economies, EU/EEA)
	Sites for which concerns are raised in the CSR