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Guidance for the preparation of good clinical practice inspections

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Guidance for the preparation of good clinical practice inspections

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1. Introduction

The scope of this document is to provide guidance for the preparation for GCP inspections carried out by competent authorities of the different Member States, which may take place on any of the following occasions:

- Before, during or after the conduct of clinical trials.
- As part of the verification of applications for marketing authorisation.
- As a follow-up to the granting of authorisation.

The guidance is applicable for inspections involving one Member State only or several Member States. When a Member State intends to carry out an inspection on its territory or in a third country with regard to one or several clinical trials which are conducted in more than one Member State concerned, it should notify through the EU portal its intention to the other Member States concerned, the European Commission and the European Medicines Agency and inform them of its findings after the inspection. In those cases where more than one Member State is involved the relevant responsibilities of the various Member States concerned are outlined in the guidance for coordination of GCP inspections requested in the context of marketing authorisation applications for mutual recognition and decentralised procedures and cooperation between the Member States. The inspections should be conducted under the responsibility of the Member State where the inspection takes place

This guidance on preparing for the inspection may be used for preparing any type of inspection (see guidance for the conduct of GCP inspections (EMA/839541/2016), including its annexes). Inspections will be prepared within the framework of this document and national procedures.

As Regulation (EU) No 536/2014 provides the basis for the application of a risk proportionate approach to the design and conduct of clinical trials, inspectors should take this into account during the inspection when such an approach is implemented in the conduct of the clinical trial inspected. Risk adaptations should be clearly described and justified in a risk assessment and mitigation plan (see reference v for further information).

2. Inspection initiation

Prior to, or during the process of requesting, or assigning, a GCP inspection, informal contacts and assessments within or between Member States (phone, fax, email) and an evaluation of the EU clinical trial system/ national inspection databases could help to define the context of the request/assignment. A decision on the scope of the inspection, the centres/sites and the composition of the inspection team will also have been made. This will lead to the definitive inspection request/assignment. In those cases where more than one Member State is involved the appointment of the inspection team and acceptance of each role is part of the guidance for coordination of GCP inspections requested in the context of marketing authorisation applications for mutual recognition and decentralised procedures and cooperation between the Member States.

The involved Member State inspectorate(s) will subsequently designate the lead inspector (LI) and the other members of the inspection team. In those cases where more than one Member State is involved and more than one site is inspected, a reporting inspector (RI) could be appointed. Further guidance on the acceptance of this role is outlined in the guidance for coordination of GCP inspections conducted for MRP and DCP procedures (EMA/431276/2016). In this latter case, communication between the RI

and the LI(s) will result in the definition of the site inspection team and formal assignment of the LI(s). The language of the inspection at each site will be in general the local language.

The dates and places for the inspection of each site are set by the LI(s) according to the national procedures. The LI(s) communicate this information to the RI, when applicable, who checks that the formal timelines are adhered to. Subsequent changes in the composition of each national team should be communicated to the RI.

At the moment the formal inspection request/assignment is issued, the LI(s) or RI, when applicable, would have been appointed, arrangements/contracts between the involved parties (i.e. Member State Inspectorates for joint inspections, etc.) would have been drawn up and contact points within the inspectorate(s) would have been identified.

The LI(s) or the RI, when applicable, formally receives a copy of the inspection request/ assignment. This is the formal start of this guidance for the preparation of the inspection. The preparation of the inspection should be completed within a deadline according to the national procedures.

A contact point at the sponsor/applicant should be identified. The inspection will be announced to the sponsor/applicant in writing and additional documents/information requested (see more details in section 7). To note that in some cases inspections may be unannounced.

3. Review of documents and information

Essential information and documentation required for preparing the inspection need to be identified, obtained and reviewed. The information needed to conduct the inspection, may be derived from a number of sources e.g. the inspection request, marketing authorisation dossier, reference documents, guidelines, legislation, inspection Standard Operating Procedures (SOPs) (EU, national), international standards (ISO/NEN), national legal requirements (EU, third country), local field standards, additional documents requested from the sponsor/ inspectee etc. A list of documentation that may be used for review prior to the start of an inspection is available in the appendix 1 to this procedure. Consultation with e.g. clinical assessors involved in the clinical trial application or marketing authorization application, or GMP inspectors (if the scope of the inspection covers IMP) may be sought.

This information should be reviewed and evaluated by the LI(s) and by the RI when applicable. The inspection request should be evaluated on the basis of the applicable/ available documents and information. Results of this review will be incorporated into the inspection plan(s).

In case the sponsor/applicant fails to provide the inspection team with the requested documents, or the submitted documentation is below the required standard, these objections will be notified to the sponsor/applicant in writing, with a deadline for remedial action. If a response is not received, the necessary measure should be taken according to the national procedures.

The review of information on all aspects of the inspection could lead to the identification of additional technical and logistical needs (e.g. translation in case of language problems, transport feasibility), or other sites requiring inspection to achieve the objectives of the request.

In addition, as a result of the review of the documentation the inspection team members may conclude that additional (external or internal) expertise is necessary to complete the inspection teams at the various sites. The information on the formal acceptance and the composition of the complete inspection team(s) will be added to the inspection files.

For each item it should be checked, if applicable, how data was generated, collected, reported, analysed, modified and archived.

4. Inspection request validation

If the review of information and documentation results in a requirement for modification of the original request/assignment (scope of the inspection, sites for inspection, timelines), this must be communicated to the people responsible for the request/ assignment of this inspection and the reasons substantiated according to the national procedures. This change must be agreed by all parties involved prior to incorporation into the inspection plan(s).

5. Inspection filing and archiving

The LI(s) participating in the inspection have to open local inspection files. When a RI is appointed, he/ she should also start the preparation of the central inspection file for the inspection as soon as the inspection is initiated. The format of these files should be in accordance with the format set out in the guidance for record keeping and archiving of documents obtained or resulting from the good clinical practice inspection.

6. Inspection plan

An inspection plan will be prepared for the inspected site to be used as an aid for the inspection team. In those cases where a RI is appointed, a central inspection plan should be prepared by the appointed RI and finalised in agreement with the LIs. Based on the central inspection plan, the LIs will prepare local inspection plans for each selected site. The level of details in these inspection plans may vary. Routine inspection requests may need less detail than for cause inspections, or inspections for specific products or systems.

The inspection plan(s) will generally outline and define the relevant aspects of the clinical trial site(s) and scope that are to be covered during the inspection at the selected site(s). It will be based on the inspection request/assignment and the reviewed documentation.

The inspection plan(s) will incorporate the timelines for the practical organisation of the inspections at the site(s), the timelines for the preparation of local report(s), whereby the integrated inspection report (IIR), if applicable, will have to be finalised according to the guidance on coordination/ co-operation with other organisations.

A checklist may be designed as part of the local inspection plan.

Elements to be taken into account when drafting the inspection plan are listed in Appendix 2.

7. Inspection announcement

The inspection team may announce the inspection to the applicant/ sponsor (contact point). In such a case the responsible personnel of the selected site(s) will also be informed of the forthcoming inspection according to the procedures of the Member State Inspectorate. In some cases however, inspections may be unannounced.

Inspection date(s) for the selected site(s) are communicated to the site(s), in accordance with the timelines in the site inspection plan(s). The relevant parts of the inspection plans will be communicated to the responsible personnel at the site.

Occasionally the sponsor/MAH may ask for a pre-inspection meeting to discuss the scope of the inspection. The LI(s) or, RI when applicable, are under no obligation to agree to such a meeting. In

case the LI(s) or, RI when applicable, feel that a pre-inspection meeting would be useful (particularly to clarify aspects of the scope for a complex inspection), they have the discretion to arrange such a meeting as long as it does not affect the overall timelines for the inspection and the sponsor/MAH undertakes to pay the additional costs. The scope of the inspection as defined in the inspection request should not be affected by the results of this meeting.

8. Practical preparation

The extent of preparation may differ between inspections, depending on the type of inspection, type of trial, therapeutic area and product, location of the inspection, number of selected sites, etc.

For EU inspections, the LI may facilitate the practicalities for the other team members as much as possible.

For third country inspections it may be convenient if the sponsor or applicant company helps with the provision of air tickets, local transport and accommodation according to the itinerary set out by the inspection team according to the MS's national procedures

For third country inspections it may be essential to establish contact with the local inspectorates/ authorities to inform them of the proposed inspection.

There may also be a need to ensure the availability for a translator. The sponsor may be requested to provide this service.

9. Responsibilities

9.1. Responsibilities of the lead inspector (LI)

- To communicate with the parties involved in the request/ assignment for the inspection.
- To verify the location of the site(s) and for the co-ordination, organisation and validation of the inspection team.
- To prepare the local inspection plan.
- To prepare, upkeep, quality and security of the local inspection files and to keep the archives according to the local procedures.
- To start the preparation of the inspection after formally receiving a copy of the request/ assignment according to the set procedures.
- To propose and set the timelines for the inspection activities (preparation, conduct, reporting).
- To initiate the formal information flow to the inspection team.
- To review the quality and completeness of the information.
- To send the submitted documentation and information to the inspection team without delay.
- To decide whether more information is needed from those parties involved in the request for the inspection.
- To conduct the inspection at the site in accordance with the local SOPs and legal requirements.
- To check that the timelines are kept throughout the duration of all inspection facets.

- To check that the confidentiality requirements are adhered to.
- To keep the inspection documentation up to date and secure.
- To ensure that all local relevant reference documents are available and important local details/ differences communicated to the inspection team.

9.2. Responsibilities of the reporting inspector (RI), when applicable

- To communicate with the parties involved in the request/assignment for the inspection.
- To verify the location of the site(s) and for the co-ordination of the inspection team.
- To prepare the central inspection plan.
- To prepare, upkeep, quality and security of the central inspection files and to keep the archives according to the local procedures.
- To start the preparation of the inspection after formally receiving a copy of the request/ assignment according to the set procedures.
- To propose and set the timelines for the inspection activities (preparation, conduct, reporting).
- To initiate the formal information flow to the inspection team.
- To review the quality and completeness of the information.
- To send the submitted documentation and information to the inspection team without delay.
- To decide whether more information is needed from the parties involved in the request for the inspection.
- To conduct the inspection at the site in accordance with the local SOPs and legal requirements (applicable when there is also LI).
- To check that the timelines are kept throughout the duration of all inspection facets.
- To check that the confidentiality requirements are adhered to.
- To keep the inspection documentation up to date and secure.

Appendix I: Documents/information that may be used for review prior to the start of the inspection

- **Inspections related documents**
  - Inspection request.
  - Inspection procedures.
  - Assessment reports, when applicable.
  - List of questions (LoQ), response to the LoQ, if applicable.
  - Pre-populated inspection report and integrated inspection report templates provided by EMA (for EMA inspections only).
- **Overview of the conduct of the study:**
  - Total number of sites/locations/ countries.
  - Inclusion rate, screening, randomisation, etc.
  - SAEs, ADRs.
  - Efficacy parameters.
  - Drop out frequency time frame of trial.
  - Annual reports, final report.
  - Presence of a similar/extension protocol.
- **Inspection sites**
  - Investigator(s)/co-investigator(s) CVs and qualifications.
  - Information on sites involved/selected (including e.g. pharmacy, clinical departments, X-ray, MRI, Echo, ultrasound, ECG, CT, CROs).
- **Laboratories**
  - Local/central.
  - Type of laboratories involved.
  - Type of examinations/tests special equipment/procedures.
- **Sponsor**
  - Responsibilities defined in contracts CRO(s) involved.
  - Protocol, amendments, investigator's brochure.
  - CRFs.
  - Patient information and consent.

- Printout (of parts) of the clinical database.
- Quality management (QC, QA).
- Sponsor SOPs related with the scope of the inspection.
- Monitoring procedures/reports.
- Monitoring plan.
- Data management plan.
- Statistical analysis plan.
- Information on electronic systems used in the trial.
- Risk assessment and mitigation plan, if applicable.

- **Trial medication**
  - GMP aspects e.g. certificate.
  - Manufacturing site information.
  - Labelling.
  - Blinding procedures.
  - Patient randomisation list/procedures (e.g. IVRS).
  - Quality documentation.
  - Batch release certificate.

- **Ethics**
  - Patient information sheet/informed consent form.
  - Patient recruitment process.
  - Insurance documents.
  - Updates of safety information/IB IEC opinion/authorisation, if applicable.

- **Applicable regulations/guidelines**
  - Applicable GCP and legal requirements.
  - Notification/approval of a trial (available in EU clinical trial IT system).
  - Importation of investigational medicinal products.
  - Announcement of inspection to the competent authority.
  - Insurance.
  - Trial medication: import license, labelling, storage, destruction.
  - SAE reporting.

- **Data**

Tabular listings of individual data:

- Data should be listed per site.
- The individual patient data listings for the patients recruited at this clinical trial site.

Appendix II: Elements to be taken into account when drafting the inspection plan

- **General aspects**
  - Scope.
  - Timelines.
  - Inspection team.
  - Expertise and other support needed.
  - SOPs.
  - Legalities.
- **General Content**
  - Agenda, dates.
  - Sites, facilities systems.
- **Specific contents**
- **Layout options**
  - Linear modules.
  - Agenda with addenda.

Appendix III: References

i. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

ii. Commission Implementing Act on Detailed arrangements for clinical trials inspection procedures including the qualifications and training requirements for inspectors, pursuant to Article 78(7) of Regulation (EU) No 536/2014.

iii. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.

iv. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

v. Risk proportionate approaches in clinical trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

vi. EUDRALEX "Guidelines for Clinical Trials", Volume 10 of the rules governing medicinal products in the European Union: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm.