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SCIENCE MEDICINES HEALTH

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Good Clinical Practice Inspectors Working Group (GCP IWG)

ANNEX V
TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE CHMP: Phase I Units

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1. Introduction

This annex focuses on the preparation of Good Clinical Practice (GCP) inspections conducted in Phase I units. The points to consider in this document are specific to investigator site inspections in these types of units and other guidance documents should be referred to for consideration of those areas common to other types of inspections, e.g. computer systems, archiving and quality systems.

Guidance on First in Human (FIH) and early clinical trials has been published, with the objective of managing and minimising potential risks to trial participants (healthy volunteers and patients) who take part in these types of trials. This guidance is listed in the references and should be taken into account during the inspection of the Phase I unit.

As the design of the protocol of a FIH varies from phase 2 and 3 studies, the focus to conduct an inspection of a FIH, especially performed at a phase I unit may be different or more specific to certain topics. For instance, appropriately trained and experienced staff are key to the safety of trial participants in Phase I units; competence should be documented and reassessed on a regular basis. Units must have appropriate emergency equipment and procedures for handling medical emergencies must be in place. These procedures should be tested on a regular basis and all staff must be trained in carrying out their responsibilities.

2. Description of procedure/ requirements

2.1. Protocol and procedural aspects

Points to consider:

- The data used to make protocol-related decisions such as dose escalation, integrated protocols (initiation of a subsequent study part, selection of doses, etc). Consider if this is adequate and as defined in the protocol (e.g. if less than a full cohort, only safety data or Pharmacokinetics (PK)/Pharmacodynamics (PD) data as well).
- QC of dose escalation data and interim safety reports. Check if the QC is documented and if it is clear what data was used to make the decision.
- Clarity of dose escalation criteria (e.g. what is expected for dose escalation, de-escalation, repeat dosing etc.)
- Clarity and definition of the stopping criteria (both safety and PK) for trial participants and study.
- Documentation and communication of dose escalation decisions (who, when, what data was used, outcome).
- Description of who is involved in dose escalation decisions (Sponsor, Principal Investigator [PI]) and if the persons in charge are appropriately qualified.
- Knowledge of the PI in relation to pharmacology of the Investigational Medicinal Product (IMP).
- Risk assessment and contingency planning e.g. sentinel dosing, emergency treatments, specialist medical staff, staffing and resources.

2.2. Ethics and regulatory approval

Points to consider:

- Independence of the Ethics Committee.
- Documents reviewed by the Ethics Committee and Competent Authority.
- Documentation of approval of activities or documents (e.g. advertising, screening procedures and associated information sheets and consent forms) and of the study.
- Process for submission for Ethics Committee and Competent Authority approvals.
- Updating and maintenance of Ethics Committee and Competent Authority documentation.
- GCP compliance statement of the Ethics Committee, where applicable in accordance with local regulations.
- List of members of the Ethics Committee.
- Annual reporting to the Ethics Committee and Competent Authority, where required according to national regulations.

2.3. Quality assurance and SOPs

Points to consider:

- Written procedures for every aspect of the study process (e.g. Standard Operating Procedures [SOPs], working instruction/practices or guidance documents; including any forms or templates).
- Organisation and independence of the QA group.
- Training on SOPs, GCP, medical emergencies, protocol and IMP (specific characteristics, target and mode of action and also if there is a specific framework for key high risk activities such as dosing, covering medical emergencies etc.) for both permanent and temporary staff.
- Audits of vendors and suppliers.

2.4. Investigator master file

Points to consider:

- Identification and use of source documents.
- Storage of medical records.
- Long-term archive arrangements.
- Documentation of meetings.
- Delegation log in place and signed.
- Use of Direct Electronic Data Capture methods (e.g. electronic Patient Reported Outcomes [ePRO] devices or bedside e-data capture systems).

2.5. Personnel

Points to consider:

- SOP for minimum staffing levels during clinical conduct and medical supervision on dosing days.
- Relationship of the Investigator with the Sponsor company.
- Adequate staff resources.
- Recruitment of staff from the facility/institution.
- Basic, immediate and advanced life support training.
- Qualifications of the Investigators (including any experience or post graduate qualifications in human or clinical pharmacology for FIH trials).
- Qualification and training of permanent and temporary staff.
- Management of permanent and temporary staff.

2.6. Facilities

Points to consider:

2.6.1. Emergency procedures and equipment

- Availability and maintenance of emergency medicines and equipment: immediate access to equipment and appropriately qualified staff for resuscitating and stabilising individuals in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), and ready availability of intensive care unit and other hospital facilities.
- Emergency contact numbers provided to the trial participants.
- Procedures in case of an emergency (including scenario testing).
- Alarm points (documented regular testing).
- Procedures and agreements with the local hospital(s)/ nearby intensive care unit for any services provided (e.g. responsibilities and undertakings of each in the transfer and care of patients).
- Fire evacuation procedures.

2.6.2. General facilities

- Security of the facility with respect to unauthorised or limited access.
- Back-up power supply.
- Storage of samples. Monitoring of the fridges and freezers.
- Maintenance, service and calibration of instruments/equipment (including emergency equipment, fridges, freezers, balances, scales, centrifuge, testing of syringe pumps/drivers prior to be used for infusions etc.).
- Facilities for archiving, laboratory and pharmacy.

2.6.3. Trial participant care

- Procedures for testing for use of illegal drugs (drugs of abuse).
- Measures in place to ensure compliance of the trial participants with the protocol.
- Monitoring of trial participants.
- Facilities for meals. Documentation of meals and compliance with any protocol exclusions.
- Leisure facilities for lengthy stays/overnight stays.
- Identification of trial participants during their stay.
- Documentation of medical history (including volunteer database or medical notes).
- Where required by local regulations and/or the protocol, documentation of request for relevant medical information from the general practitioner/ family doctor.

2.7. Sampling

Points to consider:

- Documentation of processing of samples within the unit prior to shipment to the laboratory (e.g. electronic systems, including paper backups or paper systems).
- Facilities equipped and resourced to handle the samples.
- Procedures for collection of urine samples (restricted access to toilets/showers).
- Procedures for sample management e.g. collection, processing including spinning (centrifuge), consideration for missed and late samples, aliquoting, labelling, tracking, storage and shipment.
- Clocks – easily visible and synchronised.

2.8. Investigational medicinal product

Points to consider:

- Authorisation/Licence(s).
- Blinding, if applicable.
- Storage and access control.
- Packaging and labelling.
- IMP administration.
- Compliance with the randomisation list, if applicable.
- IMP accountability (including receipt, dispensing, returns, quarantine and destruction).

2.9. Recruitment and consent

Points to consider:

- Recruitment strategies.

- Volunteer database.
- Collection and verification of the trial participants medical history.
- Contact with the trial participant's primary physician/family doctor.
- Procedures to prevent 'over-volunteering'.
- Routine screening procedure (including any counselling or procedures for handling reportable diseases e.g. for positive serology results).
- Trial participant records.
- Procedures taken to verify the identity of the trial participants.
- Procedures for payment.
- Procedures for taking consent (including verification that trial participants have understood the information).

2.10. Contracts

Points to consider:

- Contracts in place prior to study start.
- Management and documentation of collaborations with other departments/organisations.

2.11. Insurance and indemnity

Points to consider:

- Provisions in place for insurance and indemnity.
- Indemnification of the investigator (e.g. professional indemnity, etc.).
- Professional indemnity insurance for nurses, if applicable.

2.12. Confidentiality

Points to consider:

- Confidentiality agreements for temporary staff, consultants etc.
- Procedure to ensure trial participant personal identifiers do not leave the unit (e.g. on sample labels, adverse event documentation etc.).

2.13. Adverse events

Points to consider:

- Ensure there is an agreement with sponsors detailing notification of PIs immediately of new safety/toxicology data.
- Recording of adverse events.
- Follow-up and counselling.

- SUSAR reporting to Ethics Committee/Regulatory Authorities.
- SUSARs information provided to investigator(s).

3. Forms needed for this procedure

Not applicable.

4. References

General documents applicable to all trials:

i. EMA/CHMP/ICH/135/1995: "Guideline for good clinical practice".

ii. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products EMEA/CHMP/SWP/28367/07, current revision.

Documents applicable to trials conducted under the Clinical Trial Directive:

i. Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

ii. Annex 13 to the EU Guidelines to Good Manufacturing Practice.

Documents applicable to trials conducted under the Clinical Trial Regulation:

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. National and local requirements relating to Part II of the application dossier.

iii. Detailed Commission guideline of 8 December 2017 on the good manufacturing practice for investigational medicinal products pursuant to the second paragraph of the Article 63(1) of Regulation (EU) No 536/2014.

iv. Commission Implementing Regulation (EU) 2017/556 of 24 March 2017 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council.