AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

# Phase I Clinical Trial Inspections

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# Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

| Interessi nell'industria farmaceutica | NO | Attualmente | Da 0 a 3 anni precedenti | oltre 3 anni precedenti |
|---|---|---|---|---|
| *INTERESSI DIRETTI:* | | | | |
| 1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica | X | ☐ | ☐ | ☐ obbligatorio |
| 1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico | X | ☐ | ☐ | ☐ obbligatorio |
| 1.3 Impiego per una società: altre attività | X | ☐ | ☐ | ☐ facoltativo |
| 2. Consulenza per una società | X | ☐ | ☐ | ☐ facoltativo |
| 3. Consulente strategico per una società | X | ☐ | ☐ | ☐ facoltativo |
| 4. Interessi finanziari | X | ☐ | ☐ | ☐ facoltativo |
| 5. Titolarità di un brevetto | X | ☐ | ☐ | ☐ facoltativo |
| *INTERESSI INDIRETTI:* | | | | |
| 6. Sperimentatore principale | X | ☐ | ☐ | ☐ facoltativo |
| 7. Sperimentatore | X | ☐ | ☐ | ☐ facoltativo |
| 8. Sovvenzioni o altri fondi finanziari | X | ☐ | ☐ | ☐ facoltativo |
| 9. Interessi Familiari | X | ☐ | ☐ | ☐ facoltativo |

* Angela Del Vecchio, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 25.03.2015 e pubblicato sulla Gazzetta Ufficiale del 15.05.2015 in accordo con la policy EMA /626261/2014 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. <Per questo intervento non ricevo alcun compenso>

# References


- ABPI Guidelines for Medical Experiments in Non-Patient Human Volunteers, 2007
- Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (CHMP/SWP/28367/2007)
- Procedure for conducting GCP inspections requested by EMEA: phase I units (annex V), 23 July 2008

# Scope of Phase I Inspections

- routine system inspections of Units conducting Phase I trials to ensure Units maintain satisfactory standards for avoiding harm to trial subjects and for handling medical emergencies should they arise
- standard expectation applied to all Units carrying out trials other than FIH trials
- additional requirements for Phase I Units wishing to carry out trials with compounds at all levels of risk

# Inspection Process Overview

Inspection would include:

- Opening Meeting
- Staff Interviews
- Facility Tours
- Documentation Review
  - SOPs and Study Procedures
  - Study Specific Documentation
- Closing Meeting

# System Inspections (1)

## Clinical Tour

- To include clinical wards, subject recreation areas, kitchen, pharmacy, and sample processing laboratory
- Focus on:
  - Emergency medicines and equipment
  - Unit security and emergency procedures
  - Sample management
  - IMP storage and dispensing
  - Equipment calibration and maintenance

# System Inspections (2)

## General Facilities

- What procedures are in place to ensure security of the facility with respect to unauthorised access. What measures are in place to contain volunteers during their stay i.e. no access to offices, kitchen, laboratory, pharmacy.
- Is there a back-up power supply for the Unit and emergency lighting
- Where are samples stored? Are the fridges and freezers monitored and alarmed
- How are instruments/equipment maintained, serviced and calibrated? Is it labelled appropriately?
- What facilities are available for archiving, laboratory and pharmacy. Are there SOPs to cover all aspects of the clinical trial in these areas.

# System Inspections (3)

## Volunteer Care

- What are the procedures for illegal drugs testing (drugs of abuse)? Any random tests during the study?
- What measures are in place to ensure compliance of the volunteers with the protocol e.g. search and restriction of volunteers' possessions to prevent disallowed concomitant medication and foods.
- How are subjects monitored – is there a central nurse's station where all beds can be viewed? Are Closed Circuit Televisions (CCTV) in operation?
- What are the facilities for meals – are specialist meals prepared for certain studies i.e. high fat, is a dietician involved. Is the documentation adequate, can the degree of protocol compliance be established
- What leisure facilities are available for lengthy stays/overnight stays
- How are subjects identified during their stay (wristband IDs, cards) What checks are made before each blood draw and drug administration?

# System Inspections (4)

## Medical Care of Subjects

- Physicians' oversight and role in study
  - Medical cover (24-hours)
  - Eligibility
  - Adverse events
  - Emergency unblinding
  - Role in dose escalation decisions
- Nurses role in screening, dosing, source document completion and CRF completion
  - Process for delegation by the PI
  - Sample processing

# System Inspections (5)

## Recruitment and Screening

- Recruitment and advertising (How are volunteers contacted, does the unit have a 'pool' that it draws from -What is involved in the routine screening procedure – who performs this (physician and /or nurse- What records are kept of volunteers that are screened, and those who take part in research
- Subject identification throughout the study (What steps are taken to verify the identity of the volunteers and how is this checked during stays in the unit).
- Confirmation of medical history (How are volunteer histories taken and verified)
- Informed consent (What are the procedures for taking consent – is this done individually, or as a group. Do volunteers have sufficient time and access to the staff for questions in order to make an informed decision).
- Procedures for preventing over-volunteering (What steps are taken to prevent 'over-volunteering. How are volunteers informed of the dangers of over-volunteering).

# System Inspections (5)

## Recruitment and Screening (cont.)

- Site volunteer database, how is this managed, what considerations are made for confidentiality validation, if required.
- Contact with the subject's primary physician/family doctor (in order to notify them of the subject's participation and in order to ascertain if there are any reasons that the subject should be excluded from the study ).
- Where applicable, check of national volunteer databases to ensure that the subject is not or has not recently been participating in a clinical trial. How does the unit ensure that vulnerable subjects are not enrolled.

# System Inspections (5)

## Recruitment and Screening (cont.)

- Is counselling provided for virology screening, where necessary
- How are subjects informed if they are not suitable for a study
- Payment (-what procedures are followed to determine payment to the volunteers, are reserve subjects paid - is this reviewed by the Ethics Committee. How are pro rata payments determined)
- What training has the recruitment staff received in order to deal with volunteers' questions.

# System Inspections (6)

## Emergency Procedures and Equipment

- What emergency medicines and equipment are available (as per local resuscitation guidelines) –
  - Blood pressure monitoring and recording equipment
  - Continuous multi-lead ECG monitor with facility for permanently recording any trace
- There should be a trolley in each main area, that can be moved quickly to where it is needed. Emergency trolley should carry:
  - Oxygen and delivery apparatus
  - instruments for procedures such as intubation, emergency tracheostomy and canullation
  - suitable fluids for IV infusion
  - Ambu bag, or equivalent, for assisted ventilation
  - Aspiration equipment
  - Defibrillator

# System Inspections (6)

## Emergency Procedures and Equipment (cont.)

- Contents of the trolley should be checked weekly, and the checks documented. Expiry dates for medication on the trolley should be checked regularly and documented. If the trolley is sealed then the tamper proof seal should be checked weekly.
- Beds – able to be tilted and adjusted for height
- What consideration is given to provision of emergency contact numbers to the volunteers while they are outside the unit
- How are medical staff called in an emergency – where are the alarm points (showers, toilets, in the ward area) Can staff open bathroom doors from the outside in an emergency
- Is there an agreement with the local hospital for any services provided
- Is there a hospital with an accident and emergency service close by? How easy is it to get a subject out if seriously ill i.e. in a stretcher – wide corridors, steep stairs without access to a lift. Is there access for an ambulance
- Fire evacuation procedures during study activities e.g. transfer of subjects whilst undergoing infusion

# System Inspections (7)

## Personnel

- Is there an adequate staff rota in place to ensure that there is appropriately qualified staff on site during volunteer stays, and in particular during dosing days.
- Who has basic life support and advanced life support training
- What qualifications do the Investigators have:
  - medically qualified and registered to practice in the relevant area/country
  - post graduate qualifications
  - how many years post-graduate experience
  - any previous experience in the pharmaceutical industry
  - any specific training in therapeutic areas
  - GCP training

# System Inspections (8)

## Sampling

- Samples are often processed within the unit prior to shipment to the laboratory – how is this documented and tracked (outlying or unusual results may be traced back to errors in processing).
- For complex studies, or those with a large number of subjects, are the facilities equipped and resourced to handle the capacity of samples.
- What procedures are in place to handle to collection of urine samples. For example reminders may be placed on toilet doors to ensure subjects collect their urine in the required container. Toilet doors may be locked, therefore ensuring that subjects are required to collect a key and the urine container from staff.
- What procedures are in place for sample management e.g. collection, processing, consideration for missed and late samples, aliquoting, labelling, storage and shipment
- Clocks – are these easily visible in the wards and areas where blood will be drawn, are they synchronised. How are they maintained, is there an SOP to cover time recording e.g. how are seconds rounded up/down, what point in the blood draw is the time point taken

# System Inspections (9)

## Investigational Medicinal Product

- Is the appropriate licence in place (e.g. manufacture, import)
- How is blinding assured with respect to PK studies
- Where are the drugs stored, is there a dedicated pharmacy, who has access to this. Are there adequate facilities for storage and dispensing. What are the requirements for release of IMP to the Unit
- If bulk supply is divided up in the clinic, what are the procedures and documentation for this, and for labelling. What quality controls checks are performed
- What checks are performed to ensure that medication has been taken e.g. mouth checks

# System Inspections (10)

- Contracts and Agreements
- Project Management
- Data Management, Statistics & Medical Writing
- Information Systems
  - IT systems, security, back up
  - Validation of computer systems
  - Review of systems for Direct Electronic Data Capture
- Trial Master File & Documentation Review
  - Trial Master File/Investigator File Review for 2 or 3 selected studies
  - Including review of CRFs and Source Notes for selected Subjects

# System Inspections (11)

## Quality System and Archiving

Written procedures for every aspect of the study process. SOPs should include:

- Transfer of subjects to hospital
- Out of hours medical cover and contact with Sponsor or IMP responsible person(s)
- Training and refresher training in emergency resuscitation procedures
- Procedures for common medical emergencies e.g. syncope, hypotension, anaphylaxis, cardiac arrest.
- Unblinding in an emergency
- Subject recruitment
- Informed consent
- IMP Management (including receipt, accountability, return to the sponsor, packaging if applicable)
- Investigator Master File and archiving
- Frequency of audits, results, reports and follow-up, trend analysis
- Archiving retention policy, process and control
- Visit to on-site archive if applicable to review environmental conditions.

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