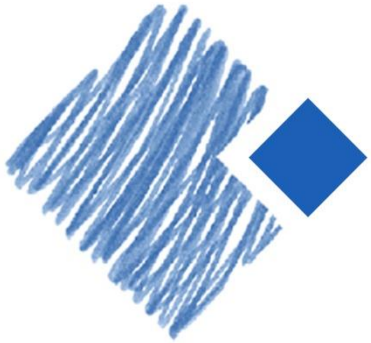

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GCP and GMP inspections in phase I: what can be learned?

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GCP/ (GMP) inspections in Phase I

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A CRO´s perspective

- avoidance of findings
- preparation of an upcoming inspection
- intercultural differences: EU, FDA and ANVISA – some typical characteristics
- examples: findings typical for phase-I
- trends

Avoidance of findings

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General strategy

- learnings from internal QC and self-detected deviations
- learnings from internal audits
- learnings from numerous sponsor audits
- learnings from inspections
- learnings from conferences

Continuous improvement of the QMS

- learnings translated into processes
- training and SOP adaptation

Internal knowledge management needed !

Preparation of an inspection

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Some important points to be considered

- management of documents
  - prior to inspection submission to inspector as requested
  - fast retrieval during the inspection
- training
  - dos and don´ts as general rules to be explained
  - study / project specific training
- logistics
  - adequate space and comfortable working atmosphere
  - easy copying and … do not forget the copy tracking !
  - designated minute-taker for continuous reporting of Q&As
  - designated and experienced lead-auditee responsible for co-ordination
  - CRO management on-site available
  - sponsor in background available

Preparation of an inspection

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Further important points

- recapitulation of chronology of events in the study
  - amendments / note to files
  - deviations
  - Serious Adverse Events
- background information
  - communication plan and vendors / subcontractors involved
  - contracts
  - internal audits/ monitoring reports

Check TMF and subject / patient files!

Training

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Important take-home messages

- clear and precise answers - sparing use of words
- in the case of uncertainty: wait with the answer until you have checked the documents
- do not speculate – no assumptions!
- do not intentionally delay submission of documents
- do not intentionally retain information
- always tell the truth
- in case of language problems – use an interpreter!

Be self-confident! Do not forget:
You are a professional and you are doing a good job!

European GCP Inspections

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General attitude

- often a very cooperative relationship
- often meeting on an equal footing
- often a strong focus on subject´s rights
- often a strong focus on training and qualification

Trends observed (personal impression)

- picky control of clear demarcation of responsibilities in the meantime also in GCP inspections
- increasing focus on the sponsor´s role
- increasing focus on data protection
- critical attitude toward electronic data capture

FDA investigators

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General attitude

- often very distanced
- often in search of fraud and misconduct (in phase I also towards the participating subjects)
  - example: imputation of hidden food under a not screwed suspended ceiling
- formally focused on tracking of samples and IMPs in the CPU
- bioequivalence trials: responsibility for the IMP affiliated to the investigator

ANVISA inspections

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General attitude

- often in search of fraud and misconduct
- driven by the experience of a developing country
  - high level of criminality (focus on burglary protection)
  - low level of public health care system
  - unstable power supply
  - frequent vermin infections
- often not familiar with a high educational level of the auditee's staff especially for nurses and other clinical staff / technicians

1. Pitfall example in phase I

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Problems associated with phase-I-setting: example ICF

- ICF-version mix-up when ICF print done by the nurse is not controlled
- ICF mix-up when several studies are run in parallel
- ICF-missing time of signature although first measures are done on the same day

2. Pitfall example: detailed protocol

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- *"blood samples should be withdrawn at the time point planned in the study protocol and scheduled time points should be met as precisely as possible"*
- *"any deviation from scheduled sampling time point exceeding 3 minutes shall be considered as protocol deviation"*
- *"sodium-EDTA tubes shall be used"*
- *"immediately after withdrawal sampling tubes shall be placed in an ice bath with 0°C"*
- *"within 30 minutes after withdrawal centrifugation shall start in a centrifuge pre-cooled to 4°C"*

To be considered already during validation of the analytical method

Example for protocol requirements

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- *"centrifugation shall be realized at 2000 g for a minimum of 10 minutes in order to separate plasma from corpuscular components"*
- *"plasma shall be pipetted into 2 aliquots each containing a minimum of 1.5 mL plasma"*
- *"within 60 min after withdrawal samples shall be deep-frozen"*
- *"samples shall be stored at temperatures below -20°C until analysis"*

Not identical with rotation speed (RCF depends on rmp, r and ω)

Requirements seem meaningful, but are they really well chosen?

Consequence: Procedures at the CPU

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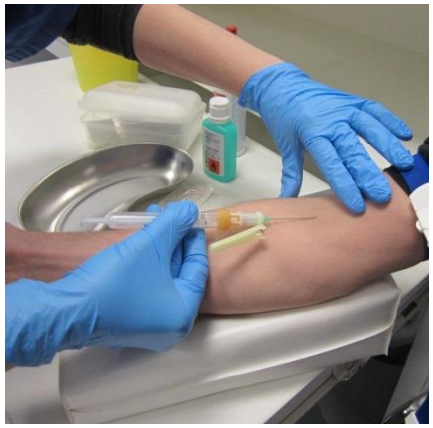
blood collection → cooling → centrifugation → pipetting



1. **data set**

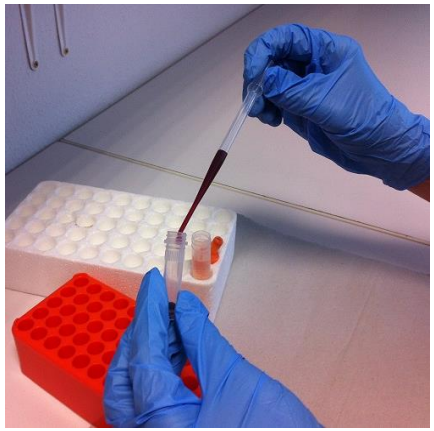
into heparinized tubes

2.

ice water bath
immediately after
withdrawal
temperature: 0°C

3.

within 30 min
at 2000 g for 10
minutes
temperature: 4°C



4.

into 2 aliquots

Consequence: Sample handling

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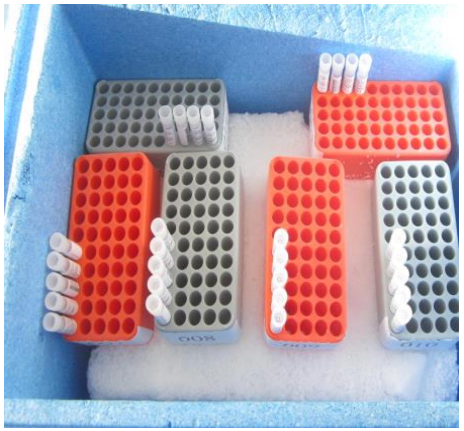
deep freezing → storage → transportation



5.

in dry ice
temperature: -78°

6.

in freezer
temperature: ≤ -20°C

7.

on dry ice
temperature: -78°

Example for protocol requirements

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What to learn from this example ?

- the protocol requirements should not be a „cook-book approach"
- instead they should define what is absolutely mandatory
- otherwise, a huge amount of superfluous data will be documented (in this case 7 data sets with a minimum of 2 often 3 or 4 separate data / numbers in total per sample)
- coming along with a high risk of inspection findings in case these requirements are applied literally by the inspectors

The risk of unnecessary findings is high in case of too detailed and superfluous protocol specifications !

Pitfalls in phase I

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3. Example: obligation to inform the family doctor

- often no family doctor available (healthy young subjects)
- and contacting often refused by subjects
- unambiguous documentation of the process is often difficult to be realised

4. Example: symptomatic subjects referred from a medical specialist or family doctor

- original patient's file not available at the site
- only anamnesis and physical examination done on site
- source data flow from physician to CPU difficult and sometimes incomplete or not correct

Conclusion

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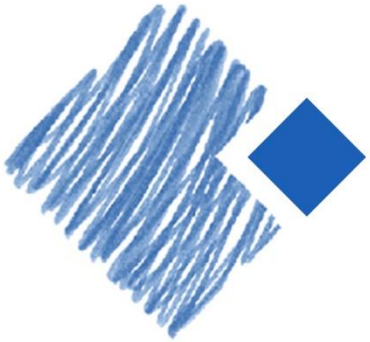
How to be successful in phase-I-inspections

- Think about the risks of findings already during set-up and document development of the trial !
- Manage your knowledge about potential findings, i.e. collect and use the experience available, work with experienced project managers, physicians and nurses !
- Prepare yourself well for the inspection !
- The CRO's inspection team should know how to behave and which rules are to be observed !
- A living Quality Management System is the best protection against inspection findings !

Success is a matter of details !



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