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Health Products Regulatory Authority

What to Expect from a Regulatory Inspection Clinical Trials

Deirdre O'Regan

GCP/PhV Inspection Manager, HPRA

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Agenda

- Inspection process
  - Planning, notification, conduct, follow up
- Commercial vs Non commercial trial inspections – points to note
- Deficiencies
  - Definitions
  - Examples
- Deficiencies noted during CRF inspections
- Possible actions following inspections
- EMA GCP Inspections
- What's changing?

Inspection Process: Planning

- Any location where trial related activities are conducted can be inspected e.g.
  - **Investigator sites**
  - Sponsor
  - Clinical Research Facilities
  - Phase I facilities
- Risk based trial selection
  - High level of clinical trial activity
  - Trial/investigator not previously inspected
  - Therapeutic area – new or of interest

Inspection Process: Notification & Conduct

- Notification
  - Approx. 4 weeks in advance
  - Includes request for documentation to be submitted prior to inspection

- Conduct
  - Approx. 3 days, 1-3 inspectors
  - Interviews, document reviews, demonstrations

Inspection Process: Conduct

- Conduct (contd.)
  - Potentially critical or major issues discussed on an ongoing basis
  - Closing meeting – preliminary findings
    - Definition of deficiency classification provided
    - Inspection findings summarised
    - Deficiencies classified as far as possible (input from HPRA experts sometimes required)
    - Questions relating to findings answered
    - Follow-up activities explained

Inspection Process: Follow-up

- Inspection follow-up
  - Inspection report issued- Day 15
  - Response to inspection report - Day 35
  - Correspondence, if necessary, to Day 80
  - Inspection close out - Day 90

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Commercial vs Non-commercial Trial Inspections

- Similarities
  - Same regulatory framework & reference standard
    - Need to ensure subject safety, data reliability and compliance with GCP
  - Same inspection objectives
- Differences
  - Interviews – different scope, one person may fulfil several functions
  - Different funding & sponsor arrangement
  - Ongoing safety evaluation considered challenging for non commercial sponsors

Deficiency Classification

- Critical Deficiency
  - Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data
- Major Deficiency
  - Conditions, practices or processes that **might** adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles
- Minor Deficiency
  - Conditions, practices or processes that **would not be expected to** adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Examples of Critical Deficiencies (Investigator)

- Protocol non-compliance
  - Assessment of subject eligibility not documented by an investigator
  - Test/procedure evaluation not done/not documented by an investigator

  Common root cause: Protocol requirements different from routine site practice

- *Expectation:*
  - *Protocol compliance is mandatory*
    - *Exceptions:*
      - *Immediate hazard*
      - *Instruction is stated as optional*
  - *Active management of deviations required, including identifying cause and actions e.g. retrain/ submit protocol amendment/improve SOPs*

Examples of Critical Deficiencies (Investigator)

- Safety reporting
  - SAEs not recorded in CRFs
  - SAE reports not subject to investigator evaluation prior to submission to sponsor
  - Inconsistent data within SAE report re causality
  - SAEs not reported within required timelines
  - SAEs not followed up within appropriate timelines
  - Attributes of AEs, including causality and severity, recorded by research nurses. Documented evidence of investigator evaluation unavailable

- *Expectation:*
  - *Evidence of investigator review of AEs, SAEs*
  - *Timely reporting and follow-up*

Examples of Critical Deficiencies (Investigator)

- Informed Consent
  - Informed consent form not signed by subjects prior to enrolment

- *Expectation:*
  - *Current version signed and dated by subject and investigator*
  - *Adequate version control of ICFs essential*

- Subjects randomised to treatment prior to HPRA trial approval

Examples of Critical/Major Deficiencies (Sponsor)

- Safety
  - Poor record keeping
    - Detailed AE records not maintained (case files and safety database)
  - Reference Safety Information (RSI)
    - Lack of tracking of RSI
    - Failure to review of impact of any changes over the course of the trial (e.g. SmPC updates)
  - Lack of processes for SUSAR identification and submission

Examples of Critical/Major Deficiencies (Sponsor)

Safety contd.

- Development Safety Update Reports (DSURs):
  - Poor quality DSURs
  - None submitted
- Lack of formalised structures for ongoing safety monitoring, for example
  - Non Compliance with protocol requirements re. frequency of IDMC reviews
  - Lack of control of data required for the IDMC and link with Clinical Data Management/database
  - CRF and clinical database not available from when first subject enrolled

Examples of Major Deficiencies (Investigator)

- Protocol Compliance
  - Non-compliance with **all** requirements e.g. all non routine lab tests not done
  - Assessment of subject eligibility not clearly documented
  - Deviations not documented with follow-up actions

Examples of Major Deficiencies (Investigator)

- Informed Consent
  - Current, approved ICF not used
  - Updates to PIL & ICF not given to subjects in a timely manner
  - Subjects did not personally date signature
  - Person taking consent not delegated to do so

Examples of Major Deficiencies (Investigator)

- Safety
  - Failure to document all adverse events
  - Records of investigator review of adverse events incomplete
  - Late reporting of SAEs from site to sponsor
  - Inconsistent data within SAE report

Examples of Major Deficiencies (Investigator)

- Data Handling
  - Subject name used as identifier on documents sent from site
  - CRFs not reviewed/signed by investigator
  - Corrections to medical data not reviewed by investigator
  - Lack of documented evaluation of test results by an investigator

Examples of Major Deficiencies (Sponsor)

- Documentation control
  - Protocols updated by means of a letter to investigators
  - Trial file
    - All essential documents not on file
- Resources and Training
  - Insufficient resources
  - No trial related training of some personnel
  - Lack of knowledge of GCP and local regulatory requirements

Examples of Major Deficiencies (Sponsor)

- Roles and Responsibilities
  - Not clearly defined and assigned
  - Review of resources/feasibility prior to site selection inadequate
    - Insufficient resources at site

- Monitoring
  - None conducted
  - Insufficient monitoring conducted
    - Monitoring plan not risk based
    - Monitoring plan not complied with
  - Deficiencies identified during inspection not identified during monitoring

Deficiencies: CRF Inspections

- Poorly defined QMS document hierarchy and management
  - Uncontrolled/ incomplete set of SOPs and record forms
    - Inadequate written procedures
    - SOPs did not reflect current practice
    - Not all practices described in controlled procedures e.g. management of biological samples, equipment servicing & calibration, oversight and management of third parties, IMP related temperature monitoring, receipt and storage
  - Non compliance with SOPs

Deficiencies: CRF Inspections

- Training
  - Requirements not defined for each role
  - Induction and ongoing training requirements and timelines not specified
  - Assessment of training effectiveness not undertaken
  - Complete training records not maintained

- Roles and responsibilities
  - Inadequate documentation of responsibilities for example for emergency services, pharmacy, monitoring, ongoing safety monitoring

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Deficiencies: CRF Inspections

- Lack of awareness of some sponsor responsibilities, for example
  - Allocation of trial responsibilities
    - Medical expertise
  - Ongoing safety evaluation

Deficiencies to Avoid!!!!!!

"A standard procedure describing the process for determining the level of benefit/risk monitoring necessary for a trial was not in place"

"The evolving risk/benefit profile of trials was not reviewed"

"Continuous monitoring relied on expedited SAE reports and DSURs, a system which did not utilise all data available to the sponsor"

"Procedures for detecting signals from safety database were deficient"

"No periodic review of SAE data except when DSURs were prepared"

- Timely detection of increased incidence of SAEs is required

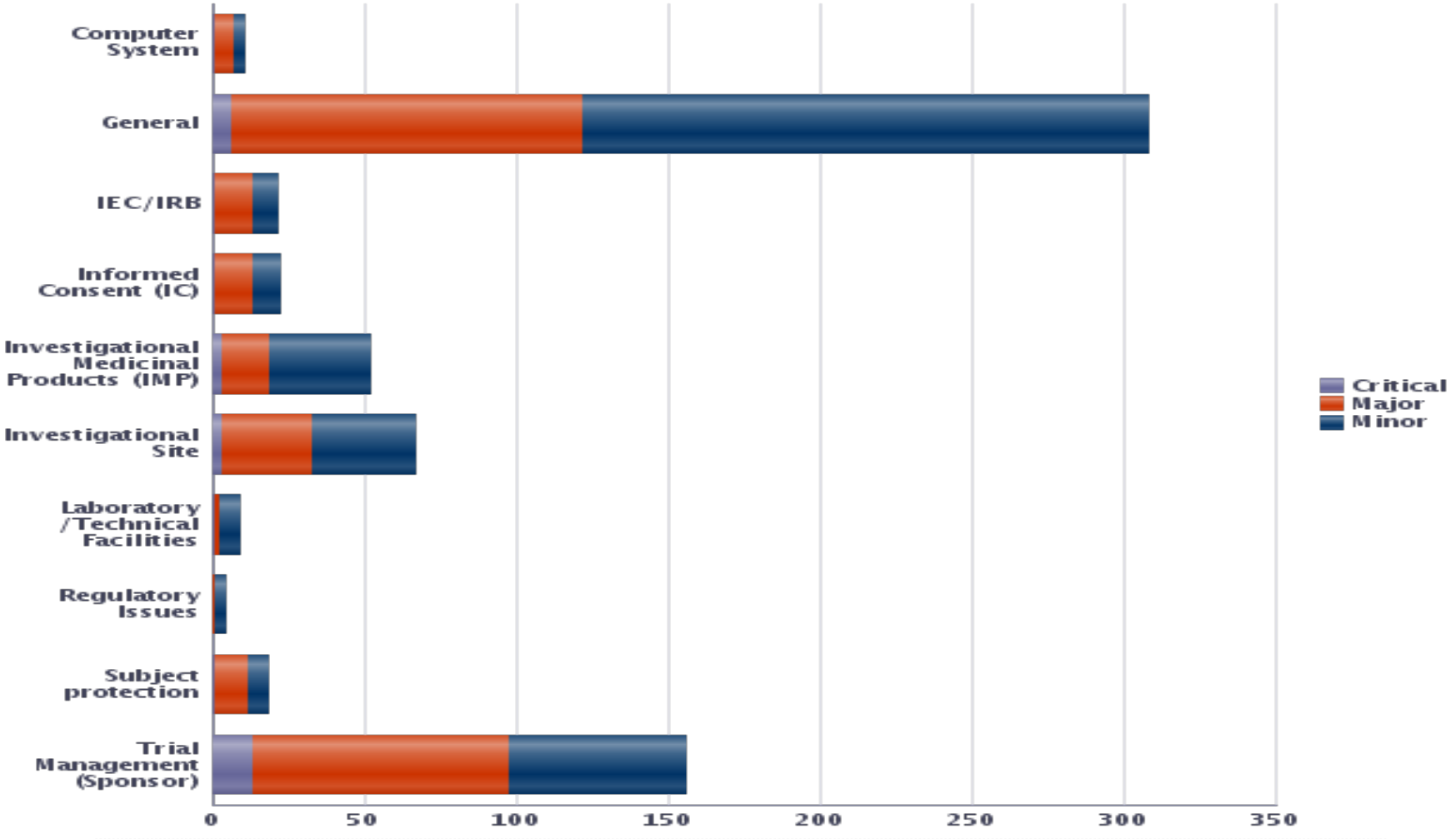
Possible actions arising from multiple major/critical deviations

- Deviations reviewed internally with representatives from Compliance, HPAR/HPM soon after inspection
  - Presentation made to HPRA Management Committee, CT Sub Committee and ACHM, if necessary
  - Recommendations regarding corrective actions/follow-up inspection
  - Possible meeting with sponsor regarding corrective action plan
  - Possible suspension of clinical trial activities

EMA GCP Inspections, 2015

- 57 CHMP requested inspections
- 673 deficiencies
  - 30 critical
  - 290 major
  - 353 minor

EMA: Findings in Main Categories, 2015 (Draft)



EMA Findings: General

- General includes deficiencies in
  - Essential documents,
  - Source documents,
  - SOPs,
  - Qualification and training,
  - Organisation and personnel,
  - Contracts/agreements
  - Facilities and equipment,

What's changing?

- ICH E6(R2)."The most substantial change to international guidelines in 20 years" occurred earlier this year when the ICH*
  - To be published in November 2016
- At about the same time the guidelines go into effect, new Clinical Trial Regulation (CTR) 563/2014 will replace the current, decade-old EU Directive 2001/20.
  - Implementation date unclear

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What's changing? New/More emphasis on ……

- Risk based trial management
- Risk based monitoring
- CRO and vendor oversight
- Control of essential documents and TMF
- New emphasis on CSV expectations
- Standards regarding electronic records and essential documents
- Additional PI oversight responsibilities at site and of vendors

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Thank you for listening

Questions?