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# Good Clinical Practice Inspections

# Expectations for Compliance with Sponsor Responsibilities, Part I

IMB Clinical Trials Seminar 19th June 2012

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# Agenda: Part I

- Inspection Team
- Overview of Legislation
- Inspections: Commercial vs Non-Commercial
- Expectations of compliance with sponsor responsibilities Part I

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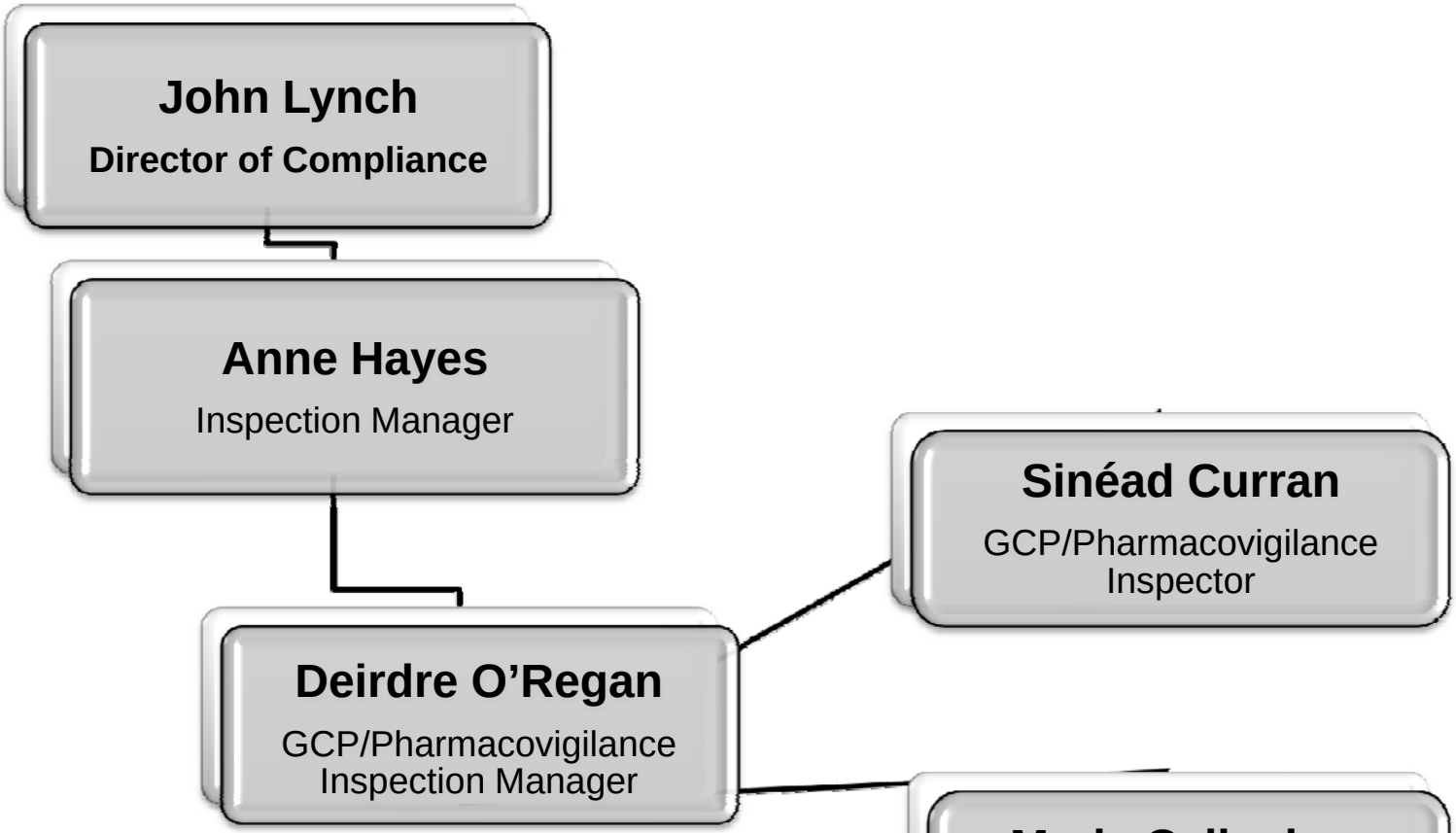
# Organogram: IMB Compliance Dept.

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# Overview of Legislation

- Directive 2001/20/EC
  - Implemented nationally into SI 190 of 2004 as amended
    - S.I. 878 of 2004 and S.I. 1 of 2009
- Directive 2005/28/EC
  - Implemented nationally into SI 374 of 2006
- Commission Directive 2003/94/EC
  - Implemented nationally S.I. No. 539 of 2007
- Regulation (EC) No.1394/2007
  - Implemented nationally S.I. No.4 of 2009 (ATMPs)

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# In summary.....

- Clinical trials are inspected against:
  - Clinical trial authorisation
  - Protocol
  - National legislation (Statutory Instruments) and Guidelines e.g.:
    - ICH GCP
    - Annex 13 of EU GMP Guide
  - SOPs

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# Commercial vs Non-commercial Inspections

- Similarities
  - Same regulatory framework & reference standards
  - Same inspection objectives
- Differences
  - Interviews – different scope, one person may fulfil several functions
  - Different funding & sponsor arrangement

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# Presentations

**Part I, Deirdre**

- QA & QC
- Training
- Agreement Management
- Monitoring

**Part II, Sinéad**

- Data Management
- IMP Management

**Requirements, *Inspection Questions*, Deficiencies Noted**

# Quality Assurance and Quality Control

- Requirements: Quality Assurance and Quality Control - ICH GCP 1.46, 1.47, 2.13, 5.1, 5.2.1, 5.18.4

*Has the sponsor implemented and maintained QA and QC with written SOPs to ensure that trials are conducted and data generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements?*

- Deficiencies frequently noted re.:
  - Implementation and management of SOPs

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# Deficiencies in SOP Management

- SOPs not available/incomplete for all tasks, for example:
  - Management of Trail Master File
  - QA and QC of critical documents e.g. protocol, PIL/ ICF
  - Pharmacovigilance (expediting and periodic reporting)
  - Monitoring
  - Data Management
  - IMP management

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# Deficiencies in SOP Management

- No procedure for preparation, review and documented approval of SOPs
- Uncontrolled distribution of SOPs
  - Current versions of SOPs not distributed and obsolete SOPs in use
  - No access to copies of essential SOPs
- SOPs not regularly reviewed and updated
- SOP training
  - Not done and documented in good time

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# Training

- Requirements - ICH GCP 2.8, 5.6.1, 5.18.2, 5.18.4, 5.19.2, 8.2.10, 8.3.5

*Are sponsor staff qualified by training and experience to perform their tasks e.g. auditors, monitors?*

*Has the sponsor ensured that the investigator and site staff are qualified by training and experience with adequate resources to conduct the trial ?*

- Deficiencies frequently noted re.:
  - Timing of training
  - Records of training

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# Deficiencies in Training

- GCP training
  - Evidence of GCP training not on file for staff
  - GCP training post-dated trial activity
  - No evidence of refresher training

- Study specific training
  - Post -dated trial activity
  - No documented evidence of training staff who join the trial when in progress
  - No documented evidence of training in updates e.g. in protocol amendments

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# Deficiencies in Training

- Inadequate systems in place for the management of training
  - Training requirements not defined re. delivery/receipt/verification of effectiveness/ training records
  - Training required for different roles not defined
  - Timelines for completing targeted training not defined
  - No system in place for the management of training files
    - Responsibilities for file maintenance not documented
    - No definition of required content

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# SOPS and Training

- ***Key message***

  - Establish SOP system and SOPs ***before*** trial activities commence & maintain the system

  - Ensure targeted training is provided and documented ***before and during*** trial

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# Agreement Management

- Requirements - 5.1.2, 5.1.4, 5.2, 5.6.3, 5.9, 5.15.1, 5.18.4h, 8.2.2, 8.2.4, 8.2.6

*Were all responsibilities clearly defined in written agreements with all parties involved in the trial e.g. investigators, CROs?*

*Were written agreement/contract signed before enactment?*

*Did Investigator/Institution agreement reference:*

- *The requirement to conduct the trial per GCP, regulatory requirements, approved protocol*
- *Direct access for monitoring, auditing and inspecting*
- *Retention of trail related documents?*

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# Deficiencies in Agreement Management

- No procedure(s)
  - To describe responsibilities for review and approval of agreements and subsequent amendments
  - To describe the process to ensure third parties implemented and maintained QC & QA re the duties/tasks transferred (Oversight)
- Agreements not signed prior to commencement of activities
- No consistent method of tracking the roles and responsibilities retained and transferred
- Procedures were insufficient to ensure that written agreements were executed – inadequate oversight

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# Monitoring

- Requirements - ICH GCP 1.38, 1.39, 2.13, 5.18, 5.20, 8.2.19, 8.2.20, 8.3.10, 8.4.5

*Did monitoring verify that:*

- *The rights and well-being of human subjects are protected?*
- *The reported trial data are accurate, complete, and verifiable from source documents?*
- *The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s) ?*

*Was the Monitoring Plan/SOP adequate for the trial and complied with?*

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# Deficiencies in Monitoring

- SOPs/Monitoring Plan relating to monitoring activities were inadequate e.g.
  - Scope and frequency of monitoring visits or a minimum frequency not specified
  - Timelines for production of monitoring visit reports and follow-up letters not specified
  - Follow-up  required in case of non-compliance not specified
  - Review of monitoring visit reports not described

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# Deficiencies in Monitoring

- Non-compliance in the conduct of the trail was not identified and documented during monitoring visits, for example
  - Ineligibility of Subjects X & Y
  - Retrospective signing and dating of ECG/lab reports by the investigators
  - Retrospective corrections to source documents
  - Discrepancies between the CRF and source documentation identified during the inspection not identified during monitoring visits

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# Agreements and Monitoring

- ***Key message***

- Agreements
  - Implement SOP on agreement preparation, review, updating and SOP to describe how oversight is achieved and documented
  - Ensure responsibilities clearly assigned in timely agreements

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# Agreements and Monitoring

- ***Key message***

- Monitoring
  - Implement effective Monitoring Plan/ SOPs
  - Ensure compliance with Plan/SOPs
  - Check compliance

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**Thank you for your attention**

**Questions?**

**Email questions to**
**inspections@imb.ie**

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