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Overview of the IMB's Approach to Inspection of Good Clinical Practice

GCP Seminar Dublin, 27th January 2010

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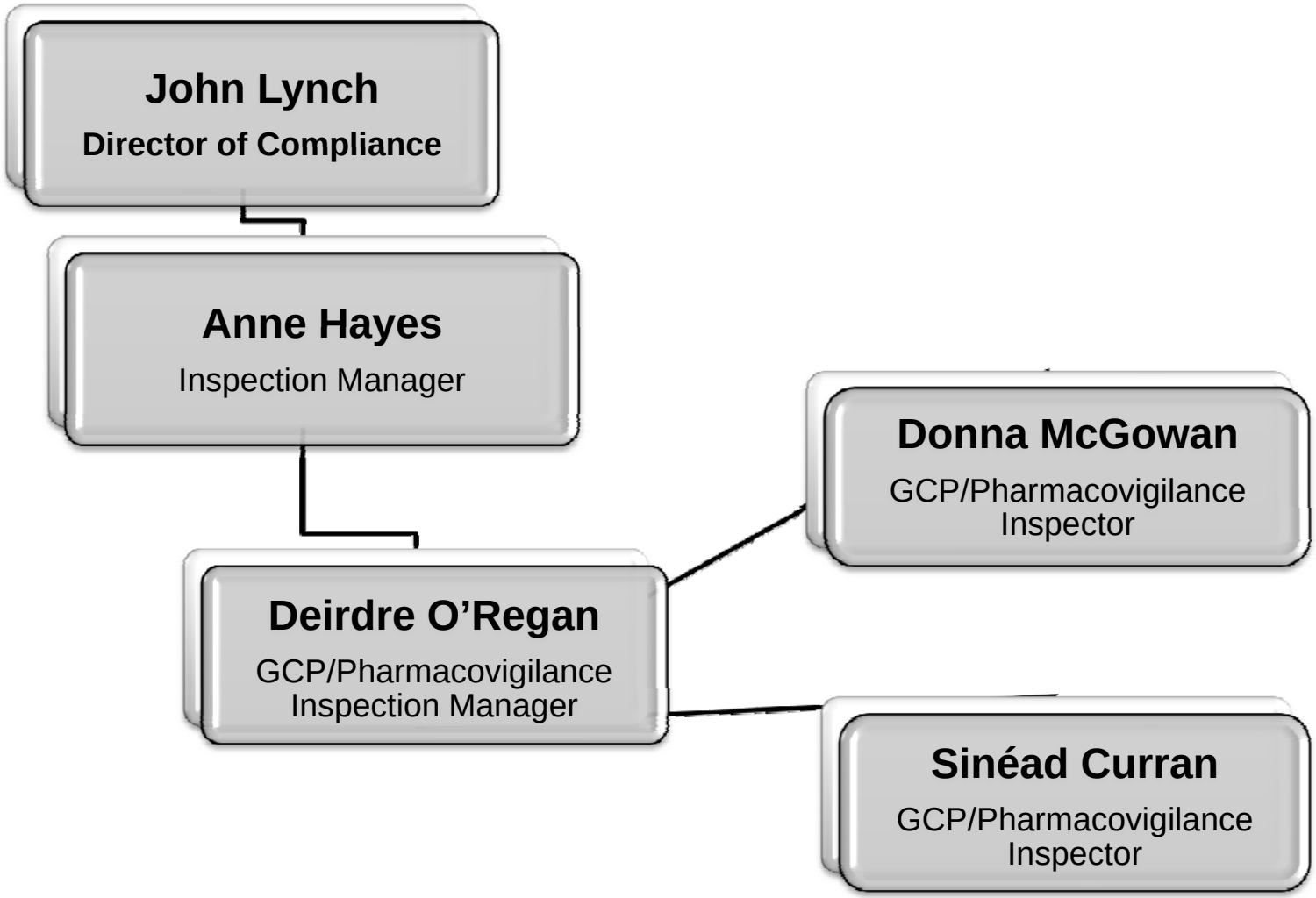
Introductions/Organisation



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Agenda

- Aims of the GCP Seminar

- Inspector Responsibilities
- Overview of Legislation and Guidance
- GCP Inspection References
- Scheduling GCP Inspections
- GCP Inspection Process

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Agenda contd.

- Classification of Inspection Findings
- Inspection Follow-up
- GCP Inspection History
- Summary of GCP Inspection outcomes 2007, 2008, 2009

- Aims of the GCP seminar

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Aims of the GCP Seminar

- Focus on investigator site responsibility (Section 4 of ICH GCP)

- Focus on areas of greatest risk

  - Legislative requirements
  - Expectations
  - Inspection findings

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Inspector Responsibilities

- Protection of public health
- Ensure that all parties involved in a clinical trial adhere to relevant legislation and guidance

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Overview of Legislation

- Directive 2001/20/EC
  - Implemented nationally into S.I. 190 of 2004, May 2004
  - Amended S.I. 878 of 2004, December 2004
- Directive 2005/28/EC
  - Implemented nationally into SI 374 of 2006, July 2006
- Regulation (EC) No. 1394/2007
  - Amended S.I. 1 of 2009, January 2009
- Guidance Documents

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Legislation & Guidance Documents

- EUDRALEX- Volume 10 Guidelines for Clinical Trials

  "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.

  - Chapter I : Application and Application Form
  - Chapter II : Monitoring and Pharmacovigilance
  - Chapter III : Quality of the Investigational Medicinal Product
  - Chapter IV : Inspections
  - Chapter V : Additional Information
  - Chapter VI : Legislation

http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm#h2-chapter-ii:-monitoring-and-pharmacovigilance

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EudraLex - Volume 10 Clinical trials guidelines - Pharmaceuticals - Enterprise and Industry - Microsoft Internet Explorer
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Reference documents
EU Legislation - Eudralex
Vol 1: Legislation Human
Vol 2: Notice to Applicants Human
Vol 3: Guidelines Human
Vol 4: GMP Human & Veterinary
Vol 5: Legislation Veterinary
Vol 8: MRL Veterinary
Vol 9: Pharmacovigilance Human & Veterinary
Vol 10: Clinical Trials
EudraLex on CD Version 21 - September 2009
Vol 6: Notice to Applicants Veterinary
EudraLex - Volume 10 Clinical trials guidelines
On this page:
Chapter I: Application and Application Form
Chapter II: Monitoring and Pharmacovigilance
Chapter III: Quality of the Investigational Medicinal Product
Chapter IV: Inspections
Chapter V: Additional Information
Chapter VI: Legislation
Volume 10 of the publications "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.
Chapter I: Application and Application Form
General information [375 KB] (July 2006)
Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial [334 KB] (revision 2 of October 2005)
Annex 1 : "Clinical trial application form" [226 KB] (revision 2 of October 2005)
Annex 2 : "Substantial Amendment Form" [136 KB] (revision 2 of October 2005)
Annex 3 : "Declaration of the end of the trial" [104 KB] (revision 2 of October 2005)
Annex 1 revised [86 KB] (revision 4 of December 2009)
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GCP Inspection References

- Clinical trials are inspected against:
  - S.I. 190 2004 (amendment S.I. 878, 2004), SI 374 of 2006, S.I.1 of 2009
  - Guidelines e.g.:
    - Note for Guidance on Good Clinical Practice: Consolidated Guideline (ICH Topic E6, Step 5) CPMP/ICH/135/95
    - EU Guideline for GMP: Annex 13: Manufacturing of Investigational Medicinal Products (Directive 2003/94/EC)
    - Commission guidelines
  - Study protocol
  - Clinical trial authorisation

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Scheduling GCP Inspections

- Current procedure for selection of sites for routine inspection:

  - Risk Based
    - Trial/sponsor/investigator/subcontractors not previously inspected
    - Geographical spread/therapeutic area
    - High level of clinical trial activity

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Scheduling GCP Inspections

- Who/what can be inspected? All locations where trial related activities are conducted e.g.
  - Sponsor/CRO sites
  - Investigator sites
  - Phase I facility
  - Clinical laboratory sites
  - IMP Manufacturing/packaging sites

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Scheduling GCP Inspections

- Types of Inspection:
  - Routine
    - Majority, to standard procedure
  - Follow-up
    - Corrective, preventive actions followed to closure
  - For-cause
    - Suspicion of fraud; the existence of adequate facilities; Clinical trials started without authorisation; Protocol amendments not approved by the IMB and/or Ethics Committee prior to enactment; Inadequate safety reporting; Inappropriate IMP manufacture, importation or management
  - European – co-ordinated by European Medicines Agency

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GCP Inspection Process

- Sponsor contacted 4 – 6 weeks prior to proposed inspection
- Inspection plan prepared
- Announcement letter & inspection plan to sponsor, including request for information
- Approx. 3 days at Investigator site

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GCP Inspection Process

- Opening meeting
  - Require Investigator to be present at opening and closing meetings
- Tour of facilities
- Review of clinical trial records
- SDV of approx. 10% of subjects
- SAE reporting

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GCP Inspection Process

- Searching, thorough & a learning experience!!
- Notify inspectees of major and critical deficiencies on an ongoing basis
- Closing meeting
  - Definition of deficiency classification provided
  - Inspection findings summarised
  - Deficiencies classified as far as possible (Input from IMB experts sometimes required)
  - Questions relating to findings answered
  - Follow-up activities explained

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Classification of Inspection Findings

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

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Inspection Follow-up

- Inspection follow-up re. major/minor deficiencies
  - ➢Deficiency Summary Report - Day 15
  - ➢Report issued - Day 28
  - ➢Response to inspection report - Day 43
  - ➢Correspondence, if necessary, Day 44 – Day 80
  - ➢Inspection close out – Day 90

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Inspection Follow-up

- Possible actions arising from multiple major/critical deficiencies:
  - Deviations reviewed internally with representatives from Compliance and immediately after inspection
  - Recommendations regarding corrective actions/follow-up inspection
  - Possible meeting with sponsor regarding corrective action plan
  - Suspension of clinical trial activities

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GCP Inspection History

Year	GCP Sponsor	GCP Site	GCP Site: Non-Commercial	Phase I	EMA	*Total*
‘04	0	4	5	1	1	*11*
‘05	1	7	0	0	0	*8*
‘06	4	10	1	1	0	*16*
‘07	1	8	1	2	2	*14*
‘08	0	12	1	0	2	*15*
‘09	0	10	6	1	7	*24*
Total	*6*	*51*	*14*	*5*	*12*	*88*

Summary of GCP Site Inspection Outcomes
2007, 2008, 2009

	Critical Deficiencies	Major Deficiencies
Protocol Compliance	69.6%	19.1%
Informed Consent	-	19.1%
Safety	17.4%	15.6%

Aims of the GCP Seminar

- Focus on areas of greatest risk
  - Legislative requirements, expectations, inspection findings re…
    - Protocol Compliance…**Sinéad**
    - Safety….**Donna**
    - Informed Consent……**Sinéad**
    - IMP Management……**Deirdre**
    - Training & Delegation….**Donna**
  - Q&A after each presentation. Other queries to compliance@imb.ie

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Thank you for your attention!

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