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Good Clinical Practice Inspections

Expectations for Compliance with Sponsor Responsibilities, Part II

IMB Clinical Trials Seminar, 19th June 2012

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GCP/Pharmacovigilance Inspector

Topics

- **Clinical Trial Data Integrity**

- **Investigational Medicinal Product (IMP) Management**

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Clinical Trial Data Integrity

- Legislation/Guidance
- IMB's approach to inspection
  - Expectations
  - Key areas considered

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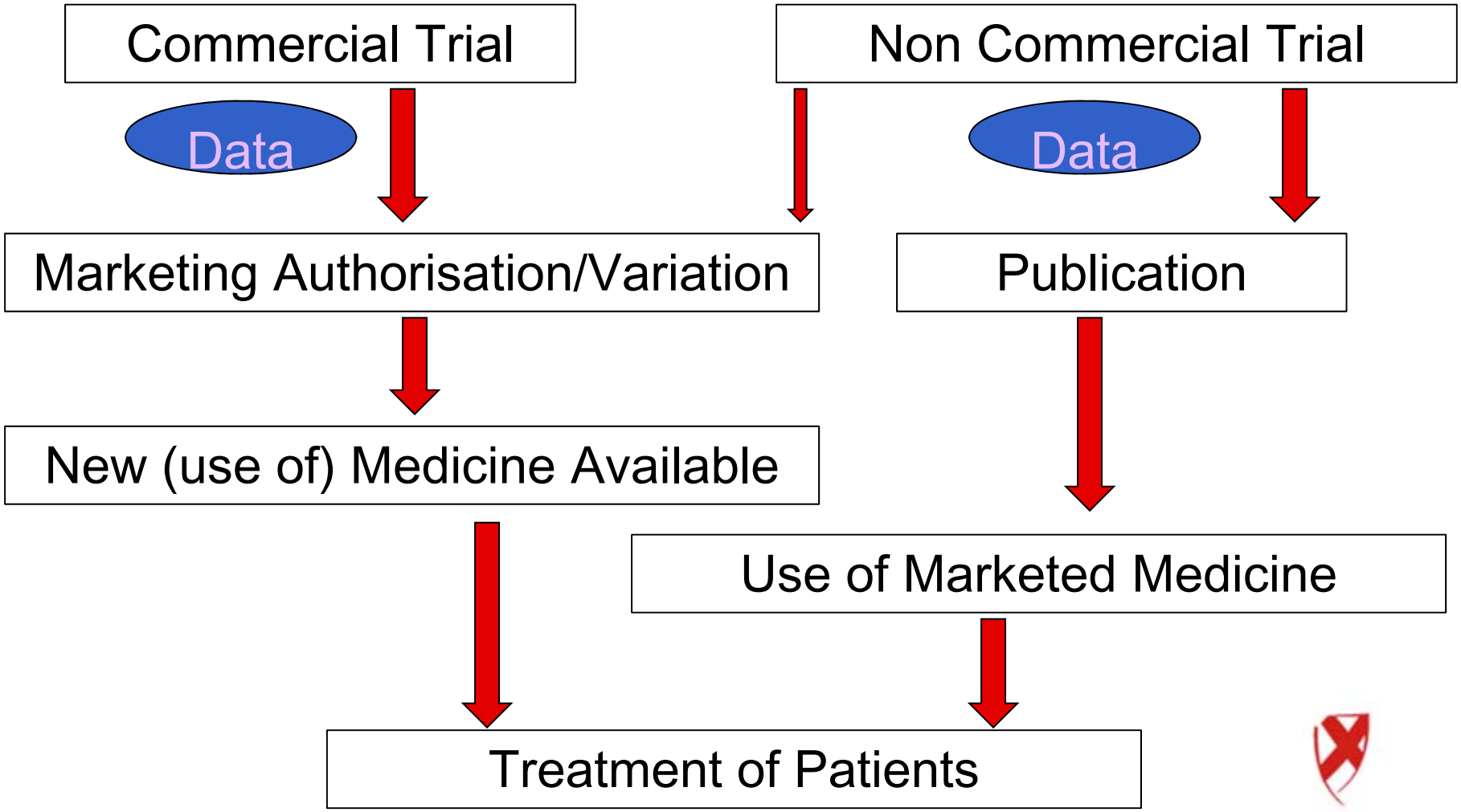
Clinical Trial Data Integrity: Key Legislation/Guidance

- ICH Guidelines:
  - Include provision for data management, analysis and reporting processes
  - ICH E3, E6 (GCP), E8, E9, E10

- Key Principle:
  - ICH GCP E6, 2.10
  - S.I No. 374 of 2006

All Clinical Trial Information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification

Clinical Trial Data Integrity



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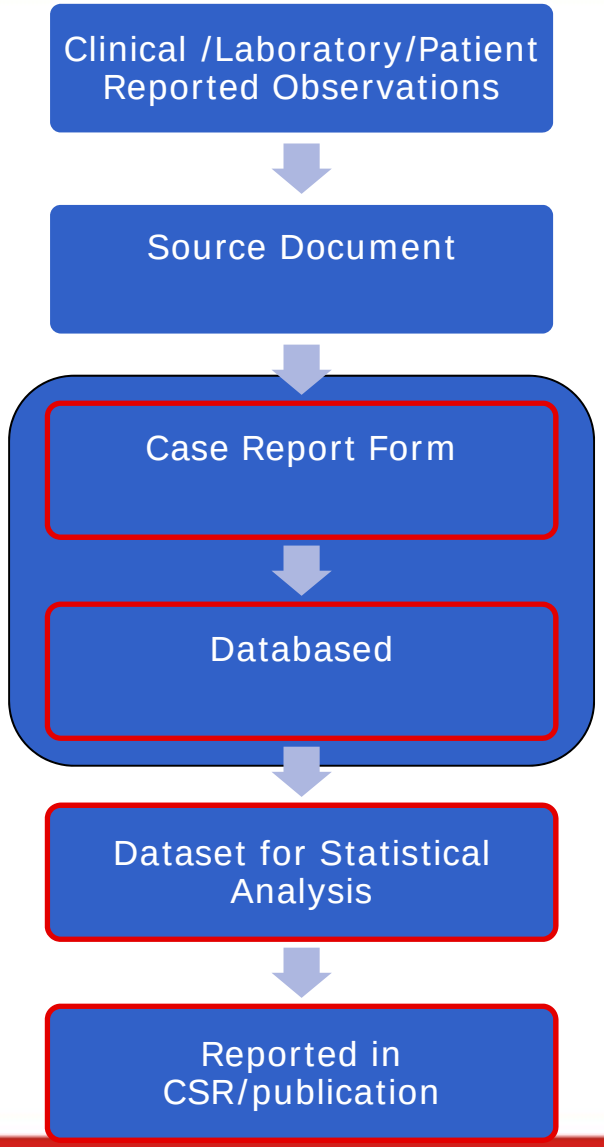
Clinical Trial Data Flow Process



- *Quality Assurance and Quality Control Systems are required at each step (ICH GCP 5.1.3)*
- *Ensures compliance with ICH GCP 2.10*
- *Complexity of data flow process, determines the level of QA and QC required*

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Inspection: Key areas considered

CRF Design

- ✓ Does the CRF reflect the protocol?
  - *Were all relevant data for analysis captured?*
  - *Was it possible to identify Important Protocol Deviations from the data captured (e.g. eligibility violators, compliance)*
  - *Was any additional data captured? – Why not in protocol?*
- ✓ Are the data entry fields adequately defined (i.e. required format/ units of measurement)?

- ✓ Was there a QC process to evaluate CRF Design?
- ✓ Was there an approval process?
- ✓ Change control?

Inspection: Key areas considered

CRF Management

- ✓ How was it ensured that staff understood how to complete the CRF?
  - *Training/User Manual*
  - *Instructions for processing data changes*
  - *Instructions for handling of missing data*
- ✓ How was it ensured that CRF data = source data? (*e.g. Training/Monitoring Process*)
- ✓ How was it ensured that all completed CRF pages were collected and included in the analysis? *e.g. Reconciliation process*
  - *No. CRF pages printed = No. of CRF pages completed + uncompleted*

Inspection: Key areas considered

CRF Management

- ✓ If electronic:
  - ✓ Validated for its purpose (storage of data only, automatic functions)?
  - ✓ Requirements of ICH GCP 5.5 complied with (SOP, audit trail, security, list of individuals authorised to make changes, back up, safeguard the blind)?

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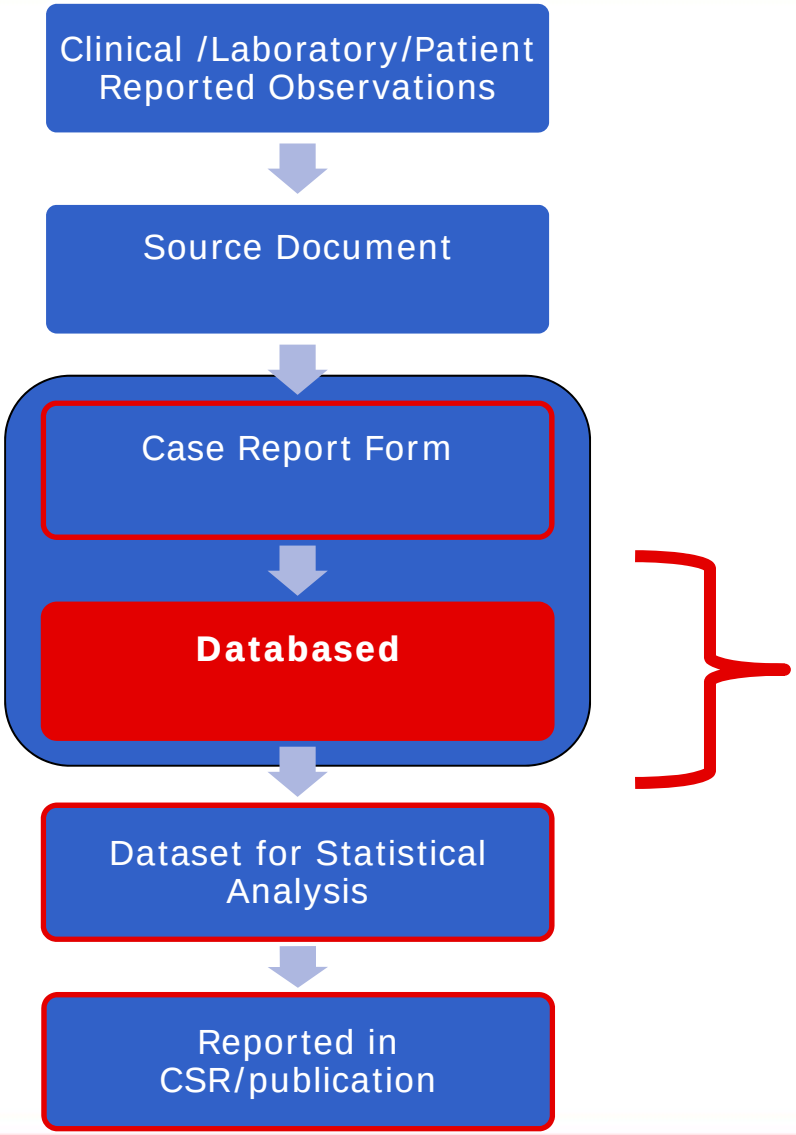
Inspection: Key areas considered



- *How was the information collated?*
- *'Clinical Database'*

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Inspection: Key areas considered

Collation of Data: Questions asked for CRF, where relevant, asked again

- ✓ Design: Data entry fields adequately defined ?
  - Focus on any data coding (MedDRA, WHO product dictionary)

- ✓ How was it ensured that CRF data was accurately and completely entered? (QC process)
- ✓ Procedure for follow up on missing/ambiguous CRF data?
- ✓ How were data migrations managed ? (e.g transfer of laboratory data)

- ✓ How was it ensured that the dataset used for analysis was complete and accurate? 'Database lock' process
  - How defined, controlled, approved, recorded
  - Timing:
    - Interim and Final
    - Prior to unblinding or comparison of aggregated blinded data

Inspection: Key areas considered

Data analysis

- ✓ Prospective Statistical Analysis Plan (SAP)?
- ✓ Were all analysis accounted for in the protocol and/or SAP?
- ✓ How were patient populations defined?
- ✓ How were important protocol deviations identified and considered?
- ✓ Was any data excluded? Robust justification recorded?

Reporting

- ✓ Clinical Study Report (or publication) preparation:
  - ✓ Training of personnel, QA, QC, review, approval
- ✓ How were data outputs prepared (summary tabulations, listings)?:
  - ✓ Automatic/Manual: How data selected, QA/QC processes

Clinical Trial Data Integrity

'All Clinical Trial Information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification'

(ICH GCP E6, 2.10)

Complexity of Clinical Trial Data Flow Process determines extent of QC/QA required

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IMP Management

- **Key Legislation/Guidance**
- **Typical Scenarios and expectations for compliance**
  - **Source of IMP: External to Investigator Site**
  - **Source of IMP: Internal from Investigator Site (i.e. use of marketed medicine already available)**
- **Common Deficiency: Directions for Use**

Key Legislation/Guidance

- **ICH GCP E6, 2.12 & Part 2, S.I No. 374 of 2006:** Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol

- **European Guide to GMP**
  - **Annex 13:** Manufacture of IMPs

- **Directive 2001/20/EC & S.I no. 539 of 2007:**
  - 'Authorised Manufacturing site', 'Qualified Person', 'batch certification'

Typical Scenario: IMP Sourced Externally

IMP,
no marketed form

Manufacture to GMP

Marketed Medicinal Product
(sourced from EU market)

Designated IMP for trial:
Additional activities (repackaging, labeling – performed to GMP)

1st Step release: Qualified Person at Authorised Manufacturing site has certified that the requirements of Article 13.3 of Dir. 2001/20/EC have been met (GMP Related Activity)

2nd Step release: Sponsor Approval (GCP/GMP Related Activity)

Investigator site: Compliance with ICH GCP E6, 4.6
(inventory, storage, accountability, destruction and associated records etc..)

Two Step Release: 1st Step, QP Certification

- 1st Step, Qualified Person certification that requirements of Article 13.3 of Directive 2001/20/EC
  - In non commercial setting, routinely outsourced
  - Aspects considered during inspection:
    - ✓ Was there a technical agreement (Annex 13) in place with third party?
    - ✓ Has the Sponsor ensured that the details set out in the clinical trial application (CTA) and considered by the QP were consistent with what was finally accepted by the IMB?
    - ✓ Was there a process to communicate any subsequent changes in the CTA to the QP?

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Two Step Release: 2nd Step, Sponsor Approval

- 2nd Step, Sponsor Release of IMP
  - Annex 13 (43) GMP Guide
  - ICH GCP E6, 5.14.2: 'The sponsor should not supply an investigator/institution with investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies))

- Aspects considered during inspection:
  - ✓Was there a written procedure in place?
  - ✓Was it verified that all documentation was available?
  - ✓Record maintained?

Typical Scenario: IMP Sourced Internally

Marketed Medicinal Product available at Investigator site for routine use, in marketed form

IMP dispensed as required

IMP segregated stock

Additional GMP activities required (such as labeling)

- Performed at Inv. Site under Exemption (S.I 539 of 2007 (5))
- Performed to GMP standards

Investigator site (Compliance with ICH GCP E6, 4.6)

- Overlap with routine processes for marketed stock (e.g. storage)

Use of Marketed Medicinal Product as IMP

- Annex 13 (32):
  - ‘For clinical trials with the characteristics identified in Article 14 of Directive 2001/20/EC, the following particulars should be added to the original container but should not obscure the original labeling:
    - (i) name of sponsor, CRO or investigator;
    - (ii) trial reference code allowing identification of the trials site, investigator and trial subject

ARD

If labeling activity was performed at Investigator site, under exemption, how inspected?

- If labeling not performed:
  - ✓ Was there justification (Annex 13 (26))?
  - ✓ Was this documented in advance?

- If labeling was performed:

✓ Did the additional labels contain required information?

✓ Did the process ensure original label was not obscured?

✓ Who performed the activity (pharmacist [person under direct supervision], medical practitioner)

✓ Was the process adequate, for example:

- Reconciliation - All IMP labels accounted for ?
- Was there an independent check of the labeling activity?
- Training of personnel, written procedures?

Common Deficiency: Directions for Use

Annex 13, GMP: directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)

Common practice – use of Patient Information leaflet

- Warnings: e.g. Grapefruit juice, food effect
- Dosing instructions

- PIL (in isolation) not adequate for this purpose:
  - Not succinct: PIL contains all information about trial
  - Potential time difference (screening) consent and administration
  - No reminder to patient in medium/long term trial
  - Dosing instructions: Generic, no account for dose modifications

References and Queries

- http://www.irishstatutebook.ie
- http://ec.europa.eu/health/documents/eudralex/index_en.htm
- http://www.ich.org/products/guidelines.html

Any queries can be emailed to:

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Thank you