

# **MHRA GCP Inspections**

## **Clinical Data Management and Investigator Sites**

### **– Planning, Process, Findings**

**Joint Meeting ACDM / BARQA**

**Wyeth, Taplow, Maidenhead**

**9<sup>th</sup> June 2009**

**Andy Fisher, Senior GCP Inspector, MHRA**

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# Agenda



- Legal Basis for Inspection
- Types of GCP Inspection
- Overview of Inspection Process
- Inspection of Activities Relating to Clinical Trial Data
- Inspection Findings Relating to Clinical Trial Data and Investigator Sites

## Legal Basis for GCP Inspection (EU)

### 2001/20/EC Article 15

(1) To verify compliance with the provisions on good clinical and manufacturing practice, **Member States shall appoint inspectors to inspect sites concerned by any clinical trial conducted, particularly the trial site or sites, the manufacturing site of the investigational product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises.**

(5) [The] **detailed guidelines**.. on the... qualifications of inspectors and inspection procedures.... shall be adopted and revised.....

### 2005/28/EC Articles 25 – 30

Covers requirements for inspectors and inspection process etc.

## Legal Basis for GCP Inspection (UK)

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2001/20/EC and 2005/28/EC Implemented in the UK by Statutory Instrument 2004:1031 The Medicines for Human Use (Clinical Trials) Regulations 2004. and amendment SI 2006/1928

- Rights to inspect any site involved in clinical trial activities in the UK (Schedule 9, Regulation 47(1) point 7 via amendment of the Medicines Act 1968 Section 112 (1))

## Types of MHRA GCP Inspection

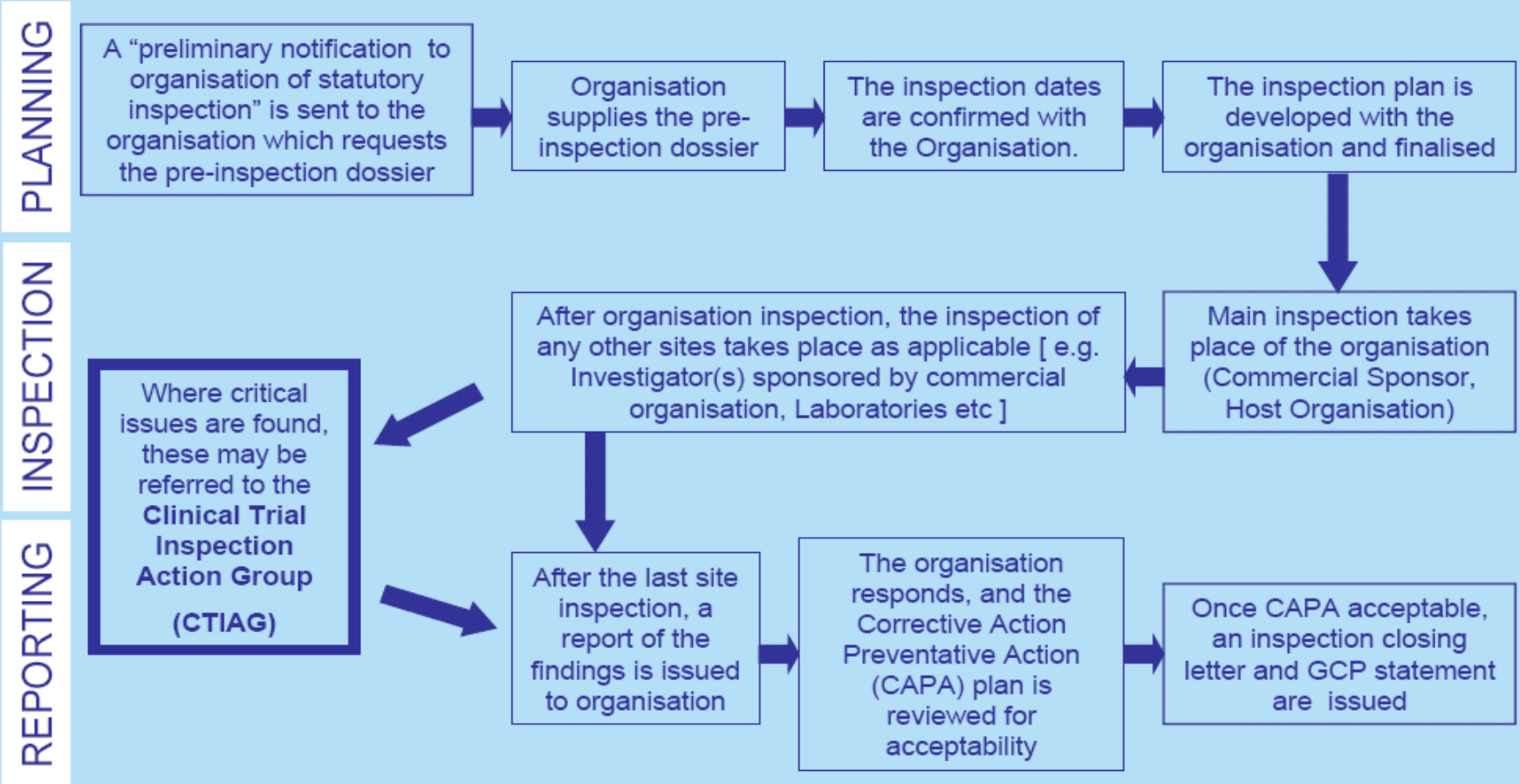
- Marketing application-related (Centralised [co-ordinated by EMEA], National requested by MHRA Assessors and occasional ad hoc collaboration between Member States)
- National Routine Systems/Routine Trial-Specific (Risk Based Programme)
- National Triggered Systems/Triggered Trial-Specific (requested by other agencies, Ethics Committees, Whistle-blowers, Serious Breaches)
- Phase 1 Voluntary Accreditation
- MHRA Inspection in a Third Country (e.g. voluntary inspections of phase 1 units in India)

# Organisations Inspected by MHRA



- Commercial Sponsors (Pharmaceutical Companies etc.)
- Non-Commercial Sponsors (NHS Trusts, Universities, Charities)
- Investigator Sites
- Subcontractors: Niche Providers, Commercial Laboratories (GCP inspections conducted by GLP Inspectorate), Phase 1 Units, Contract Research Associations (CRO)

# Routine Inspection Process



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# GCP Systems



Contract Management

Project management

**Monitoring**

Pharmacovigilance

Medical Advisors

**Data management**

**Statistical Analysis**

IMP management

Regulatory submissions

Quality Assurance

Training

**Computer systems**

**Medical writing**

Archives

Laboratories

Trial-file management for selected clinical trial(s)

**Visits to selected investigational sites**

# Inspection Process at Sponsor/CRO

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- **Opening Meeting**  
(Introductions, scope of the inspection, organisation overview, questions)
- **Facility Visits**  
(work areas involved in clinical trials, e.g., laboratories, Archives, IT, IMP, Data Management)
- **Interview Sessions**
- **Document Review**  
(Requested Documents, TMF)
- **Closing Meeting**  
(provisional feedback on inspection findings & Explain next steps)

# Monitoring, Data Management, Statistics, Medical Writing

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Typically:

- Formal interviews with appropriate staff

Visit to Data Management/Statistics department(s):

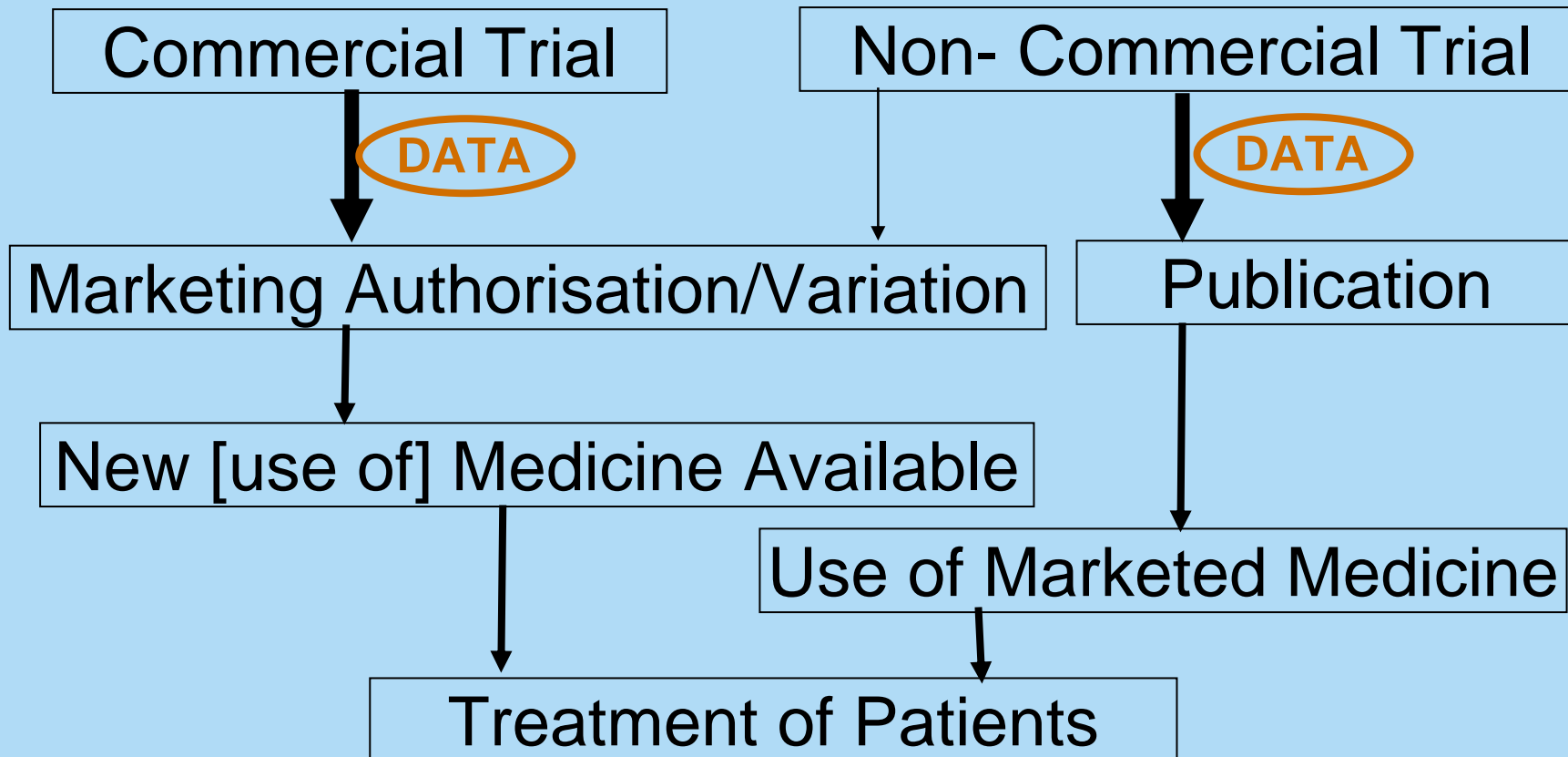
- CRF receipt/tracking/entry
- Query process
- Viewing of Database for trial/subject records
- Storage areas (CRFS, TMFs, Randomisation Codes etc.)
- Computer access to view programming/stats output/datasets etc.
- Server room

## Investigator Site Inspection

- **Planning**  
(Review of TMF, Protocol, Site Specific Documentation e.g. SOPs, **Monitoring Reports, Monitoring Guidelines**, Recruitment Figures, Delegation Logs, SAE and AE reports.)
- **Inspection Plan provided to site**  
(in advance)
- **Opening Meeting**
- **Interviews with site staff**  
(typically Principal Investigator, Sub Investigator, Research Nurse, Pharmacist)
- **Review**  
(of Investigator Site File, Consent forms, **Report Contents/CRFs and Source Data Verification [hospital notes, test results etc.]**)
- **Tour**  
(of Clinic Visit to other facilities involved in the trial)
- **Closing Meeting**

# Clinical Trial Data Integrity and Protection of Public Health

MHRA



# Clinical Trial Data Integrity

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## GCP Inspection Aim:

*To establish whether there are appropriate processes in place to give sufficient assurance that the trial data are collected, managed, analysed and reported in accordance with the approved clinical trial protocol and GCP to give credible trial results (i.e. in the Clinical Study Report [Publication])*

# UK Legal Basis Relating to Data Integrity



## UK SI 2004 No.1031 [as amended], Regulation 28:

(1) No person shall –

(a) Conduct a clinical trial; or

(a) Perform the functions of the sponsor of a clinical trial (whether the person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice.

(3) The sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of GCP are satisfied or adhered to.

## UK SI 2004 No.1031 [as amended], Schedule 1, Part 2:

### CONDITIONS AND PRINCIPLES WHICH APPLY TO ALL CLINICAL TRIALS

*Principles based on Articles 2 to 5 of the GCP Directive*

(3) Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects

(4) The necessary procedures to secure the quality of every aspect of the trial shall be complied with

(8) The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.

(9) All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remain respected.

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# UK Legal Basis Relating to Data Integrity



## UK SI 2004 No.1031 [as amended], Regulation 29:

Subject to regulation 30, no person shall conduct a clinical trial otherwise than in accordance with -

(a) the protocol relating to that trial, as may be amended from time to time in accordance with regulations 22 to 25;

(b) the terms of -

(i) the request for authorisation to conduct that trial,

(ii) the application for an ethics committee opinion in relation to that trial, and

(iii) any particulars or documents, other than the protocol, accompanying that request or that application, as may be amended from time to time in accordance with regulations 22 to 25; and (c) any conditions imposed by the licensing authority under regulation 18(2) or (6), 19(8), 20(5), 24(4 5) or Schedule 5.

## UK SI 2004 No.1031 [as amended], Regulation 29A

(1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of—

(a) the conditions and principles of good clinical practice in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25,

within 7 days of becoming aware of that breach.

(2) For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree —

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

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# UK Legal Basis Relating to Data Integrity

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## UK SI 2004 No.1031 [as amended], Regulation 50:

- (1) Any person who in the course of -  
making an application for an ethics committee opinion;  
(a) making a request for authorisation to conduct a clinical trial; or  
(b) making an application for the grant or variation of a manufacturing authorisation,

provides to the licensing authority or an ethics committee any relevant information which is false or misleading in a material particular shall be guilty of an offence.

- (2) **Any person who** -  
(a) is conducting a clinical trial authorised in accordance with these Regulations;  
(b) is a sponsor of such a clinical trial;  
(c) while acting under arrangements made with a sponsor of such a clinical trial, performs the functions of that sponsor; or  
(d) holds a manufacturing authorisation,  
and who, for the purposes of these Regulations, **provides to the licensing authority or an ethics committee any relevant information which is false or misleading in a material particular shall be guilty of an offence.**

(3) Any person who, for the purpose of being engaged as a qualified person in accordance with regulation 43, provides to the licensing authority or to the holder of a manufacturing authorisation any information which is false or misleading in a material particular shall be guilty of an offence.

- (4) In this regulation, **"relevant information" means any information which is relevant to an evaluation of -**  
**(a) the safety, quality or efficacy of an investigational medicinal product;**  
**(b) the safety or scientific validity of a clinical trial; or**  
**(c) whether, with regard to a clinical trial, the conditions and principles of good clinical practice are being satisfied or adhered to.**

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# UK Legal Basis Relating to Data Integrity

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## UK SI 2004 No.1031 [as amended], Regulation 31A:

- (1) *The sponsor shall keep a trial master file for a clinical trial.*
- (2) *The sponsor shall ensure that the trial master file is readily available at all reasonable times for inspection by the licensing authority or any person appointed by the sponsor to audit the arrangements for the trial.*
- (3) *The **master file shall at all times contain the essential documents** relating to that clinical trial.*
- (4) *The **essential documents relating to a clinical trial are those which—***
  - (a) **enable** both the conduct of the clinical trial and **the quality of the data produced to be evaluated**; and*
  - (b) show whether the trial is, or has been, conducted in accordance with the applicable requirements of Directive 2001/83/EC, the Directive, the GCP Directive and Commission Directive 2003/94/EC.*

Most guidelines within the framework of the pharmaceutical legislation do not have legal force and the definitive legal requirements are those outlined in the relevant Community legislative framework (Directives, Regulations, Decisions etc.) as well as appropriate national rules.

However, guidelines are to be considered as a harmonised Community position, which if followed by relevant parties such as the applicants, marketing authorisation holders, sponsors, manufacturers and regulators will facilitate the assessment, approval and control of medicinal products in the European Union. Nevertheless, alternative approaches may be taken, provided that these are appropriately justified.

**Structure and Content of Clinical Study Reports**  
(CPMP/ICH/137/95) ICH E3

**Good Clinical Practice : Consolidated Guideline**  
(CPMP/ICH/135/95) ICH E6 (e.g. 4.7, 4.9, 4.9.3, 5.1.1 - 5.1.3, 5.4.1, 5.4.2, 5.5.1 – 5.5.4, 5.18.3, 5.18.4 (k), (m), 5.23.2, 5.23.4, 6.4, 6.7– 6.10)

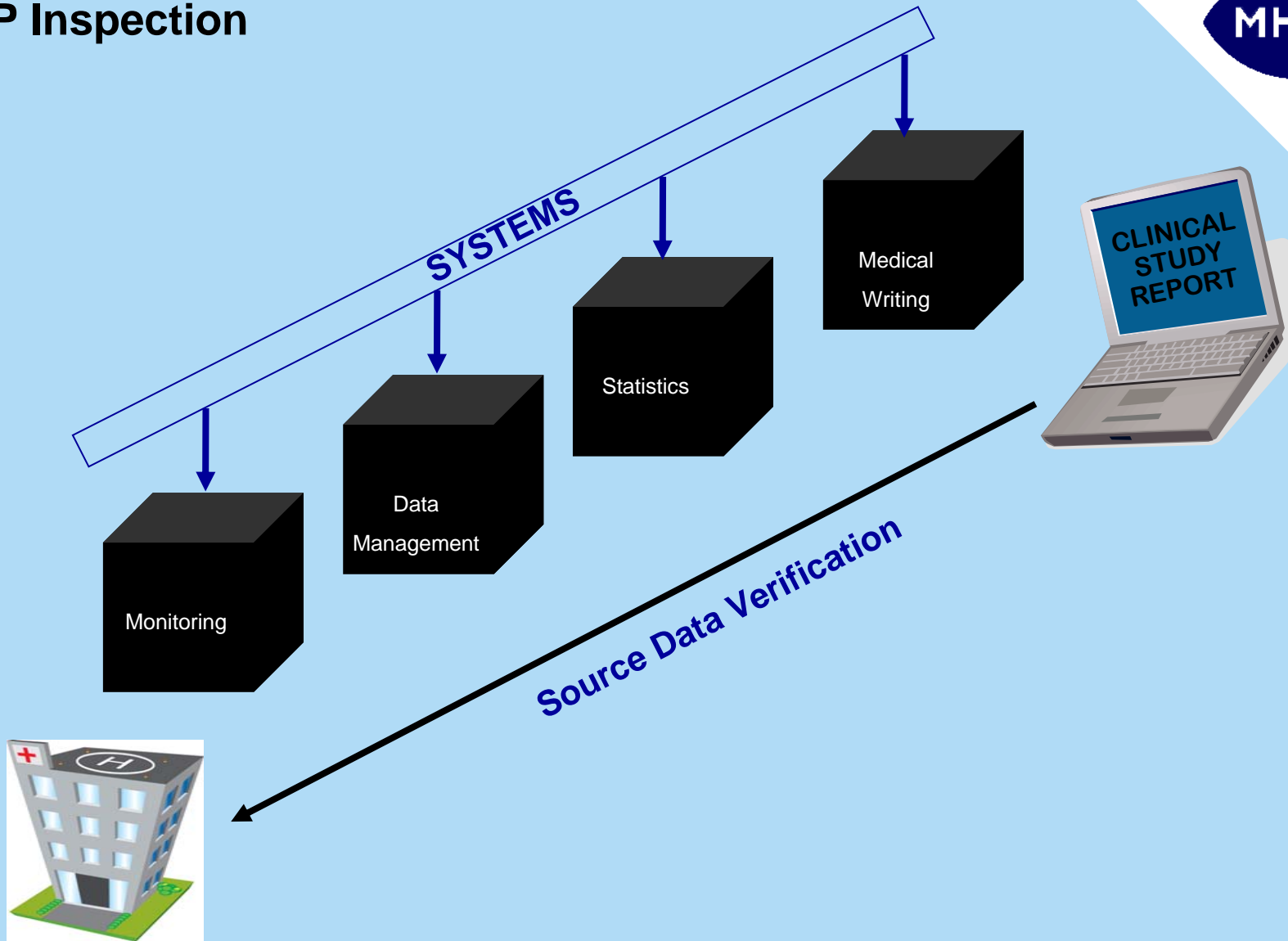
**General Considerations for Clinical Trials**  
(CPMP/ICH/291/95) ICH E8

**Statistical Principles for Clinical Trials**  
(CPMP/ICH/363/96) ICH E9

**Choice of Control Group and Related Issues in Clinical Trials**  
(CPMP/ICH/364/96) ICH E10

*Plus other detailed population/disease guidance e.g. “**E11: Clinical Investigation of Medicinal Products in the Paediatric Population** (CPMP/ICH/2711/99) ”*

# GCP Inspection



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# Inspection Findings (Clinical Trial Data)

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## Training

- Are staff appropriately trained [especially in relating to how GCP impacts on THEIR role]?

## General Data Management/Analysis/Reporting

- Is there a formalised process to control management, analysis and reporting of trial data?

## Data Collection CRF/eCRF

- How can it be demonstrated that the data being collected in the CRF (eCRF) meet the requirements of the protocol?
- Is there an appropriate review of the CRF?
- How is the functionality of the eCRF assured?

# Inspection Findings (Clinical Trial Data)



## eCRF

- How does investigator maintain an independent copy of data?
- How is it ensured that person entering data is authorised to do so?

## Database Design and Maintenance

- Is/are the data base(s) (or simple spreadsheet) used for assimilation of the data capable of collecting all the CRF/trial data appropriately?

# Inspection Findings (Clinical Trial Data)

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## Data Entry and Verification

- Is the electronic data accurate (with respect to the paper CRF and other databases)?
- How is the accuracy of the transfer of other data (e.g. laboratory) into clinical database/stats analysis package assured?
- How are changes to the data in the database after initial entry controlled?
- Are changes made to the data in the database/CRF authorised by the investigator?
- How is it ensured that subject confidentiality is maintained?

# Inspection Findings (Clinical Trial Data)

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## Data Validation

- Who reviews and approves the validation specification?
- How is the specification subject to change control?
- How is the validation programming (where used) validated and how is this documented?
- How is the validation documented?

## Data Coding

- Is it clear that queries have not been raised to change keywords to affect MedRA coding?

## Data Transfer/Release

- How is it decided when the data is ready for analysis?
- How is the final data made available (e.g. passed to the statistician) for analysis?
- How are database errors identified post lock resolved?

# Inspection Findings (Clinical Trial Data)

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## Data Quality

- Is there confidence that cross checks from the data listing in the Clinical Study Report or the Case Report Form will be verifiable with source documents?
- Is there evidence of source data verification undertaken by monitors?
- Are the electronic source documents reliable?
- Is the data in the CSR Report/Common Technical Document accurate?
- How are protocol and GCP deviations captured in the CSR?
- How is the accuracy of data to be used for dose escalation decisions ensured?

# Inspection Findings (Clinical Trial Data)

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## Statistics & Data Analysis

- Is there statistical input into the protocol (i.e. trial design) and is there a QC check of the sample size?
- How is the randomisation produced and distribution controlled?
- How is the analysis and programming checked?
- How are analysis populations decided without bias?
- Is there an audit trail in the statistical analysis?

## Interim Analysis

- Has the protocol been followed?
- Was the data monitoring committee established prior to trial commencement?

# Inspection Findings (Clinical Trial Data)



## Documentation and Trial Master File

- Can the data management and statistical processes used in a trial be reconstructed from documentation?
- Is the documentation available?

## Monitoring

- Has the data collected been verified against source data?

## Data Security

- Are the data held securely?

# Inspection Findings (Investigator Site)

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## Monitoring

- Have all hospital departments involved in the trial been visited?
- Is it possible to demonstrate exactly what date the site started to follow the new protocol following an amendment?
- Did the monitor know that the investigator site had its own SOPs? Have they been reviewed?
- Has an updated Investigator Brochure or confirmation of no update been distributed the site annually?
- Is there evidence that the annual progress report has been sent to the REC in a timely manner?
- Has the R&D department been informed of the necessary information as requested (especially protocol amendments)?
- Is there a documented report for all visits made to the site?
- Does the visit report format clearly identify issues based on seriousness?
- How have issues been escalated and resolved?

# Inspection Findings (Investigator Site)

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## Medical Oversight

- Are decisions made by Medics (PI or delegated) documented?
- What will the PI or Sub-Investigator say when asked about emergency contact provisions at an inspection?
- How would an inspector know the investigators have read the laboratory report, safety letter....?
- The PI is the only one who can access IVRS to un-blind IMP – does his/her access work?
- Are the code breaks accessible out of hours?

## Pharmacovigilance

- Have all the Adverse Events in the subjects notes been captured in the CRF?
- Were the serious Adverse Events reported according to the protocol?
- Have the Annual Safety Reports, SUSAR Line Listings been sent to appropriate authorities on time? Have the correct NRES forms been used to inform REC of information?

## Inspection Findings (Investigator Site)

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### Investigational Medicinal Products (IMP) and Pharmacy

- Does the monitor know exactly where the IMP has been stored and for how long?
- Is the IMP being stored in appropriate conditions and thermometers calibrated?
- That re-labelling procedure - would it be regarded as GMP compliant?
- Are the dispensing instructions version controlled and when they were amended were the old ones retained?
- Is the pharmacy storing and segregating the IMP according to its status?
- What documentation can be used to show who got what, where and when?
- What's the rationale for site to site transfers of IMP?

### Contracts

- Have arrangements with subcontractors been formalised?
- When the study was set up were all the necessary departments at the hospital informed?

## Inspection Findings (Investigator Site)

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### Training and Staff Delegation of Tasks

- Can it be demonstrated that all staff at the investigator site involved in the trial have had GCP training and training in UK Statutory Instrument?
- The investigators team have a weekly meeting – that's how the PI keeps up to date and staff get trained on trial procedures – how would the site demonstrate that it took place?
- Does the delegation log really show that the PI delegated tasks to trained staff BEFORE they started doing them?

### Facilities

- How can it be demonstrated that the lab manual was followed?
- Does the monitor know where the PK samples are stored and that it is appropriate storage conditions?
- That old centrifuge the nurse uses for the blood samples - has it been calibrated/maintained? What about other trial equipment?

## Inspection Findings (Investigator Site)

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### Protocol Compliance

- Has the protocol been followed and were all subjects eligible for the trial?

### Subject Recruitment & Informed Consent

- Could it be demonstrated that each subject has read the appropriate information sheet and signed the appropriate consent form at the time they were recruited?
- Have the consent forms been completed correctly?
- Is there evidence that the subjects were provided the new information/signed that new consent form in a timely manner?
- How could it be shown that the subjects' GP had been informed of their subjects' trial participation?
- Can it be demonstrated that this healthy volunteer subject actually exists?

# Inspection Reporting and MHRA Clinical Trials Inspection Action Group (CTIAG)

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- The Inspection report of all sites is usually issued to the organisation within 30 working days of the last site inspection
- Responses usually required within 30 calendar days of dispatch
- Questions and clarification, if required, but expect organisation to address findings
- Summary letter and Inspection certificate produced
  
- Referral to CTIAG for inspections with **critical** findings
  - MHRA Management level, multi-disciplinary group
  - Primary objective: protection of public health by ensuring that clinical trials of investigative medicinal products meet the required regulatory standards
  - A range of actions can be recommended by CTIAG e.g. regulatory actions (e.g. suspension of trial approval), referral for enforcement action

## Summary

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- Described legal basis for GCP inspection, types of GCP inspection and the general inspection process.
- Provided information on inspection findings relating to clinical trial data management, analysis & reporting and from investigator sites.
- Assuring the quality of clinical trial data is a key objective of GCP and the protection of public health.



# Any Questions?