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U.S. FOOD & DRUG ADMINISTRATION

Session 1: Data Integrity from International Perspectives

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FDA & MHRA GCP Workshop
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Outline

- **Background & Purpose of GCP Collaboration**

  Ni Khin, M.D., Director, DCCE/OSI, CDER/FDA

  Gail Francis, Expert GCP Inspector, MHRA

- **Quality Management System/Quality by Design (QMS/QbD)**

  Jean Mulinde, M.D., Senior Advisor, DCCE/OSI, CDER/FDA

- **Overview of Data Integrity**

  Gail Francis, Expert GCP Inspector, MHRA

- **GCP Assessment of Data Reliability in Registration Trials**

  Kassa Ayalew, M.D., M.P.H., Branch Chief, DCCE/OSI, CDER/FDA

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Learning Objectives

- At the end of this activity, participants will be able to
  - Define good clinical practice (GCP), data quality, data integrity and data reliability from global clinical trial perspectives
  - Describe GCP collaboration activities and challenges

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Background and Purpose of GCP Collaboration

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Director, Division of Clinical Compliance Evaluation
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Gail Francis
Expert GCP Inspector
MHRA/UK

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Good Clinical Practice

- GCP: International ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials

- Regulatory agencies conduct GCP inspections to ensure
  - Human subject protection
  - Data reliability
  - Regulatory compliance
  - Protection of Public Health

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Good Clinical Practice Collaboration

- EMA-FDA GCP Initiative started in September 2009
  - Joint procedures of GCP inspections established
  - Share information: common GCP issues, relevant inspection findings, etc.
  - Conduct collaborative inspections for some shared marketing applications
  - Hold bimonthly t-con meetings & GCP inspector working group discussion
  - Feasibility Pilot with PMDA/Japan

- Bilateral GCP collaboration with MHRA/UK
  - Information sharing and collaborative inspections
  - Quarterly meetings to discuss common GCP issues

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Types of GCP Inspections

EU - EMA inspections

- Part of Marketing Authorisation Application (MAA) for centralized products
- Most clinical trials have been completed
- Requested by the Committee for Human Medicinal Products (CHMP)
- Conducted by EU inspectors on behalf of EMA

National inspections

- Part of a national MAA
- Oversight of clinical trials conducted in territory
- National inspection programs

US - FDA BIMO Inspections

- Bioresearch monitoring program (BIMO)
  - An agency wide inspection program
  - Conducted by Office of Regulatory Affairs/Office of BIMO Operations Investigators
- Center for Drug Evaluation and Research (CDER) Subject Matter Expert Participation
  - Office of Compliance/Office of Scientific Investigations (OSI): GCP/PV
  - Office of Translational Sciences/Office of Study Integrity and Surveillance (OSIS): BE/GLP
  - Inspections requested by Office of New Drugs (along with Office of Clinical Pharm/Office of Biostatistics)

FDA CDER Offices (OSI & OSIS*) by Inspection Program Area

Nonclinical → **Phase 1,2,3** → **Post Marketing**

*Good Laboratory Practices (GLP)**

GCP (Sponsors, CROs, and Clinical Investigators)

Institutional Review Board (IRB)

Radioactive Drug Research Committee

*Bioequivalence/ Bioanalytical**

Risk Evaluation and Mitigation Strategy (REMS)

Post-Marketing Requirements (PMRs)

Periodic Adverse Drug Experience (PADE/PV)

Cross-functional

Risk Analysis, Risk Modeling

International Collaboration

Enforcement Policy (all program areas)

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Types of MHRA GCP Inspections

National Programme

- Risk-based: systems or study-specific.
- Triggered: systems or study-specific.
- Voluntary Phase 1 Accreditation Scheme.

Requested Inspections, MAA - related

- Requested by MHRA Licensing division
- CHMP requested (EMA Coordinated)

Joint inspections with other agencies

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Types of Organizations Inspected by MHRA

- Commercial sponsors
- Non-commercial sponsors
- Investigator sites
- Contract Research Organisations (CROs)
- Niche providers (e.g. eSystem Vendors)
- Laboratories
- Non-commercial Clinical Trial Units
- Phase 1 Units
- Bioequivalence facilities

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Types of GCP Inspections

EU - EMA Inspections

Routine

- No specific triggers identified during the MAA assessment
- Inspection selection is based on various criteria (e.g. product type, therapeutic area, target population, location of sites, sites previously inspected by FDA, etc.)

Triggered

- Scope of inspection identified during the MAA assessment
- Requested by assessors due to a concern about deviation from GCP in relation to the overall trial conduct or to the conduct at a particular site

US – FDA Inspections

Routine Data Audit

- Select sites (CI, Sponsor/CRO) from pivotal trials in marketing applications
- Most of our routine data audit inspections are of clinical trials completed and submitted in support of NDA/BLA
- Risk based site selection (using site selection tool)

For-cause

- Evaluate referrals/complaints of CI, sponsor/CRO, IRBs
- Issue inspection assignment during any phase of ongoing trials, as applicable

Surveillance

- IRB, RDRC
- Bioanalytical

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GCP Collaborative Inspections

- Joint: Both regulatory bodies are on site at the same time or at an overlapping time conducting an inspection. Both agencies follow their respective agency's process and procedures for performing inspections and produce an independent/separate inspection report accordingly.

- Observational: One of the agencies conducts a GCP inspection with observers from the non-inspecting authority present during the inspection.

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Purpose of GCP Collaboration

- To characterize and compare GCP inspection findings from entities inspected by both agencies
- To provide insight into similarities and differences between the GCP inspection findings of the two agencies
- To focus on GCP findings relevant to data reliability/integrity
- Share intelligence related to clinical trials
- Sharing of expertise, provide training opportunities
- Shared understanding of technical/compliance issues

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GCP Inspection Challenges

- Finite resources limit the number of inspections that can be conducted
- User fee timelines/accelerated approval program requires high level of efficiency for marketing applications
- Increasing numbers of
  - ➢ Sites per clinical trials
  - ➢ Trial sites outside own/familiar region (Outside NA and EU) in multi-regional clinical trials (MRCTs)

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GCP Inspection Challenges

- Novel Trial design/Methodology
  - Adaptive design
  - Pragmatic (effectiveness) trials
  - Real world evidence
  - Monitoring – Risk-based approach; Remote/Centralized
  - Clinical trials – Site centric to patient centric (Decentralized; Hub and Spoke models)
- New Technologies
  - Electronic systems such as EDC, eSource, ePRO, IRT, etc.
  - Telemedicine
  - Mobile technology

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Moving Forward

- A closer look into common GCP inspection findings (similarities and differences) in order to determine how regulatory bodies may work more efficiently to coordinate inspection efforts, when possible
- Process improvement
- Look for opportunities to provide guidance and regulatory convergence related to common GCP issues, novel trial design/methodology and new technologies

Challenge Questions

1. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials. True or False?

   Answer: True

2. GCP inspection challenges include
   a) Limited resources
   b) Timelines
   c) Novel trial designs
   d) New technologies used in global trials
   e) All of the above

   Answer: (e)

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FDA & MHRA Good Clinical Practice Workshop 2018