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HRB Clinical Research Facility Cork

PREPARATION FOR AUDITS AND INSPECTIONS

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Learning Outcomes

- Critically understand the necessity for audit and inspection of clinical trial conduct
- Appreciate the differences between audit and inspection
- Inspection types and scope
- Develop the knowledge and skills to prepare for a clinical trial audit or inspection at your research site
- Look at common findings

What is an Audit?

'A systematic and **independent examination of trial related activities** and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).' ICH GCP 1.6

- Can be part of a sponsor/CRO quality system and continuous improvement process.
  - Prepare sites for regulatory inspection
  - Training and education

- Style: Cooperative (usually!)

What is an Inspection?

'The act by a **regulatory authority(ies)** of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).' ICHGCP 1.29

- By regulatory authority to verify compliance with regulations, guidelines and Good Clinical Practice
- Can be submission driven, part of a national programme or triggered in some way
- Style: Formal

Who can carry out a Regulatory Inspection?

- Health Products Regulatory Authority (HPRA) – Authorised body in Ireland
- UK: Medicines and Healthcare Products Regulatory Authority (MHRA)
- USA: Food and Drug Administration (FDA): If the Sponsor linked to US company
- European Medicines Agency (EMEA)

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Further Information – HPRA website

Key Inspection Types

Investigator site	Sponsor site
• Generally **study specific**	• Generally **systems based**, may choose study(s) as examples
• Most **common** type of HPRA GCP inspection	• **Less common** type of HPRA inspection
• Focus upon **investigator role**	• Focus upon **sponsor role,** including quality system & operational activities
• Aspects of sponsor role also examined, in particular where there is an interface	• Most often conducted at sponsor office and/or at a CRO to whom tasks have been contracted
• Most often conducted at **clinical site**, or, an associated **research facility** where trial is conducted	

Key Inspection Types

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Clinical Trial Host

- Third party site, to whom the investigator has delegated tasks
- Newer type of HPRA GCP inspection
- Created in response development of specialised research facilities/ third party pharmacies
- Provides opportunity to broadly examine systems/processes, rather than study specific aspects
- To date, all inspections performed at clinical research facilities/centres

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Inspection Scope: Investigator Site

Organisation
e.g. delegation, personnel, training and facilities

Administrative Aspects
e.g. communication with HPRA/REC, contracts and insurance

Protocol Compliance
e.g. satisfying inc/exc criteria, adherence to schedule of assessments

Informed Consent
e.g. initial & reconsent process, use of ethics approved forms, delegated personnel, GP informed

Safety Reporting
e.g. AE Collection, assessment, recording & reporting, including SAEs

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Inspection Scope: Investigator Site

Source Doc, including SDV
e.g. ALCOAC, CRF and other reports

IMP Management
e.g. label, receipt, storage, accountability, subject compliance checks, returns, dose modifications, blinding

Clinical sample management
e.g. management of biological samples and communication of results

Investigator site files
e.g. Completeness and accuracy, archiving, computer systems

Trial Management & Monitoring
e.g. Site monitoring, SOPs, contracts, Reg/Ethics

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Types of GCP Inspection:

Inspections may be conducted on ongoing or completed studies and may be announced or unannounced.

- **Routine:**
  - Most common type, 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 HPRA and/or Ethics Committee prior to enactment;
  - Inadequate safety reporting;
  - Inappropriate IMP manufacture, importation or management

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GCP Inspection Programme

Inspections undertaken by Authorised Officers according to SI 190/2004 (as amended)

Objective of inspections is to verify compliance with regulations and relevant guidance, in particular ICH GCP E6

Inspections may take place at any location where clinical trial related activities occur

Average of 16* GCP inspections per year

*From 2008 - 2017

Also Inspected Against:

- ICH GCP Guidelines
- Legislation
- Data Protection Act
- Local SOPs
- Sponsor SOPs
- Authorisation:
  - Ethics
  - HPRA
- The Protocol!

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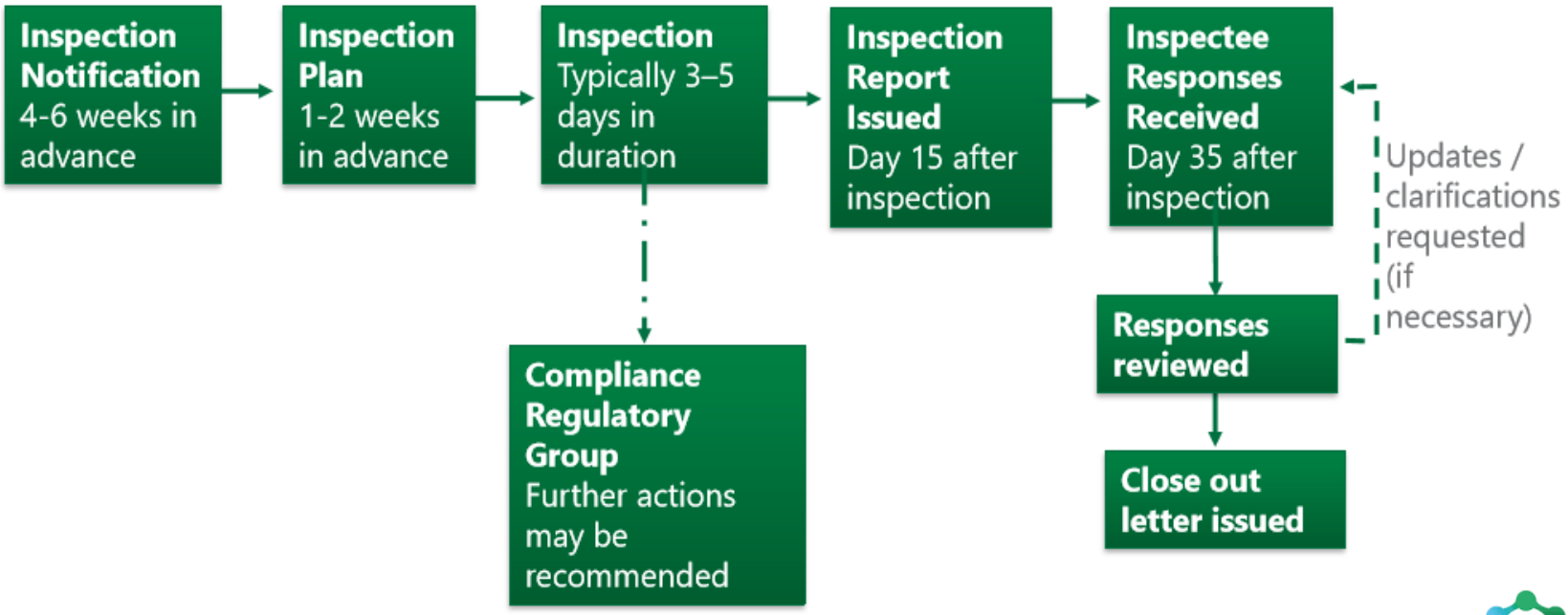
Routine Inspection Process



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Notification of inspection

The following information may be requested from the inspectee prior to the inspection:

- Participant status per trial site
- Copies of Sponsor SOPs
- Trial-specific documents
- CV of principal investigator
- Arrangements for direct access to any computerised systems
- Any other documentation deemed necessary by the inspectors
- The trial master file comprising the essential documents must be available by direct access.

Preparing for Inspection

Use run-in time to ensure that:

- Site files are complete and up to date
  - All essential documents present
  - Correct versions in use
  - All logs are completed and signed by PI
- Research staff training files are complete and up to date
  - Demonstrate compliance with site training policies and SOPs
  - Verify all personnel are fully trained in delegated duties
  - Staff members able to describe policies and processes in an interview
- Equipment records are available and contain up-to-date calibration and service records for all equipment associated with trial
- If omissions found don't cover up – implement corrective and preventative action (CAPA)

Preparing for Inspection (cont)

- Inform hospital and Institution managers of planned inspection, and given copy of agenda when available
- Facilities 'inspection ready' and available for scheduled tour:
  - Equipment present and labelled
  - Research site personnel aware of planned tour by inspectors
  - Other departments (as appropriate) aware of planned inspection and possibility of visit by inspectors (e.g. local laboratory or pharmacy)
- Medical charts available and in good condition
  - Research related documentation present and easy to locate
  - Reports (ECG, local labs etc. Appropriately filed
  - For completed studies may need to be retrieved from archives
  - For big recruitment inspectors may request specific charts in advance

Preparing for Inspection (cont)

- SOPs (site and study specific) available for inspection
  - Evidence of document management process
  - Training records aligned to currently approved SOP

- IMP Management
  - Security, storage, dispensing, accountability and destruction/return to sponsor
  - Temperature records
  - Temperature excursions
  - Be able to describe
    - Actions to be taken for temperatures deviations
    - System for quarantining IMP

Day of Inspection

- Meet inspectors/auditor at reception - Check credentials
- Orientate to Inspection room, Cloakroom facilities, café etc
- Outline department access procedures and time that services close
- A staff member - available at all times (located nearby)
- Sponsor representative
- Refreshments

Opening Meeting

- The inspection schedule will be decided by the HPRA. It starts with an opening meeting attended by the PI and all available research team members
  - Introductions;
  - Regulatory framework for inspections;
  - Scope and objectives;
  - Review inspection plan;
  - Establish official communication links;
- Site & Study overview
  - Site: number and type of studies; Previous experience of inspections
  - PI: Research experience; Overview of the study
  - Personnel: Roles and Responsibilities within the study
    - Training/experience/workload;
  - Declarations of SAEs, protocol deviations or violations

Inspection procedures

- Tour of facilities;
  - Equipment;
  - Storage/handling of IMP;
  - Storage/handling of samples;
  - Includes impromptu questions
  - May include tour of pharmacy, laboratory etc
- Review of Investigator Trial File contents
- Source data Verification (% depends on number of subjects)
- Major focus on AE/SAE reporting
- Review of SOPs and processes to ensure compliance
- Review of staff training records – relationship to delegation logs

General Instructions for all Staff

- Always answer truthfully
- Do not answer a question until you have heard and understood the whole question. If you do not fully understand what the Inspector wants, ask "Would you please restate the question"
- Answer only the question asked
- Answer questions with yes or no whenever possible
- Do not answer questions outside your area of responsibility
- If you do not know the answer to a question, state that you do not know the answer, do not speculate.

General Instructions for all Staff

- Speak clearly, slowly and at a reasonable volume
- Beware of pauses – don't rush to fill them!
- Beware of being asked the same question twice in different ways or by different inspectors.
- Do not bring documents in to the inspection area that have not been requested
- Dress professionally
- Request to have a colleague present if an unexpected interview occurs

Close-Out Meeting

- Attended by PI and staff from introductory meeting
- Be prepared to discuss comments
  - Clear up any misunderstandings and provide evidence of CAPAs
- Definition of deficiencies classification provided
- Inspection findings summarised
- Deficiencies classified as far as possible (Final classification occurs at HPRA head office)
- Questions relating to findings answered
- Follow-up activities explained

Issuance of a report

- Closing meeting - verbal overview of the preliminary deficiencies noted
- A written report issued within 15 days from the last day of inspection
- Written reports are issued in paper format, and an electronic copy is sent to a nominated contact via Eudralink
- Responses to the report should be provided within 30 working days of the date of issue with corrective and preventative action and a timeline for completion of those actions
- Once all findings and observations of the inspection have been addressed satisfactorily, the inspectee will be advised that the inspection is closed

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CAPA Expectations

- Identify and address the root cause to prevent future occurrences
- Developed in consultation with PI & all relevant personnel
- Clearly define section/personnel responsible for implementing actions
- Outline key steps required to implement the CAPA
- Include specific due dates which are reasonable and achievable
- Check for effectiveness after implementation
- Documentation and evidence available for review at future inspections or audits

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Questions?

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Common Findings From Audits and Inspections

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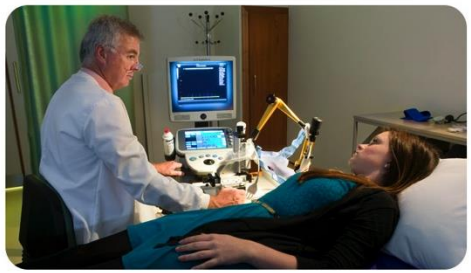
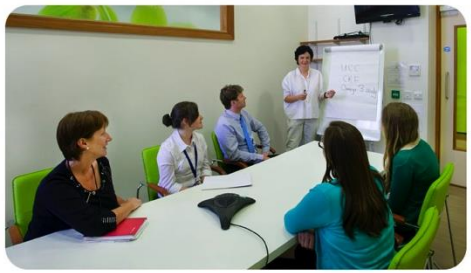
13th June 2019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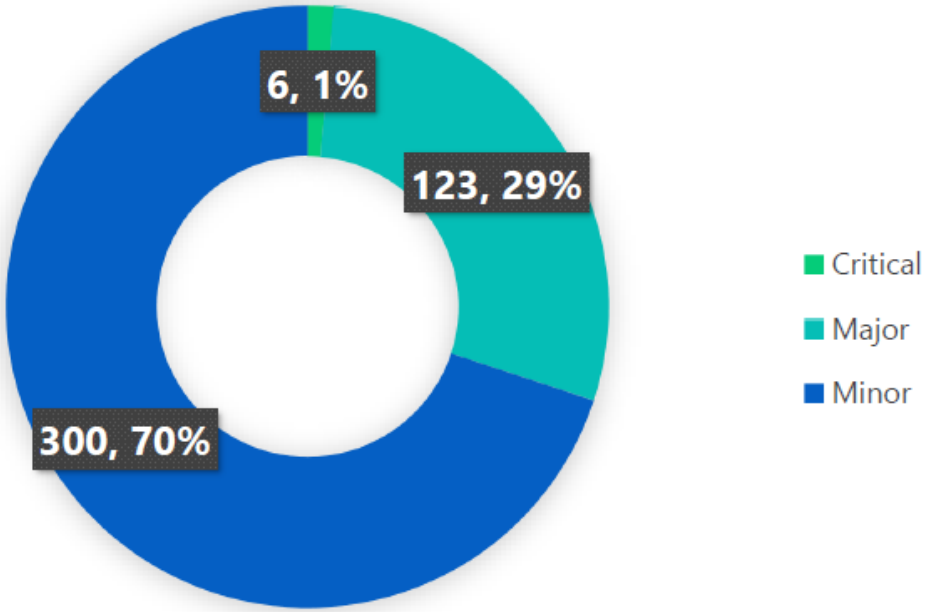
Classification of Inspection Findings

Critical Deficiency: "Conditions, practices or processes that adversely affect the rights, safety or well being of subjects and/or the quality and integrity of data."

Major Deficiency: "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 Deficiency: "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."

Inspection Findings (n=429): by Grade



Findings By Area (≥Major) Investigator Site Inspections

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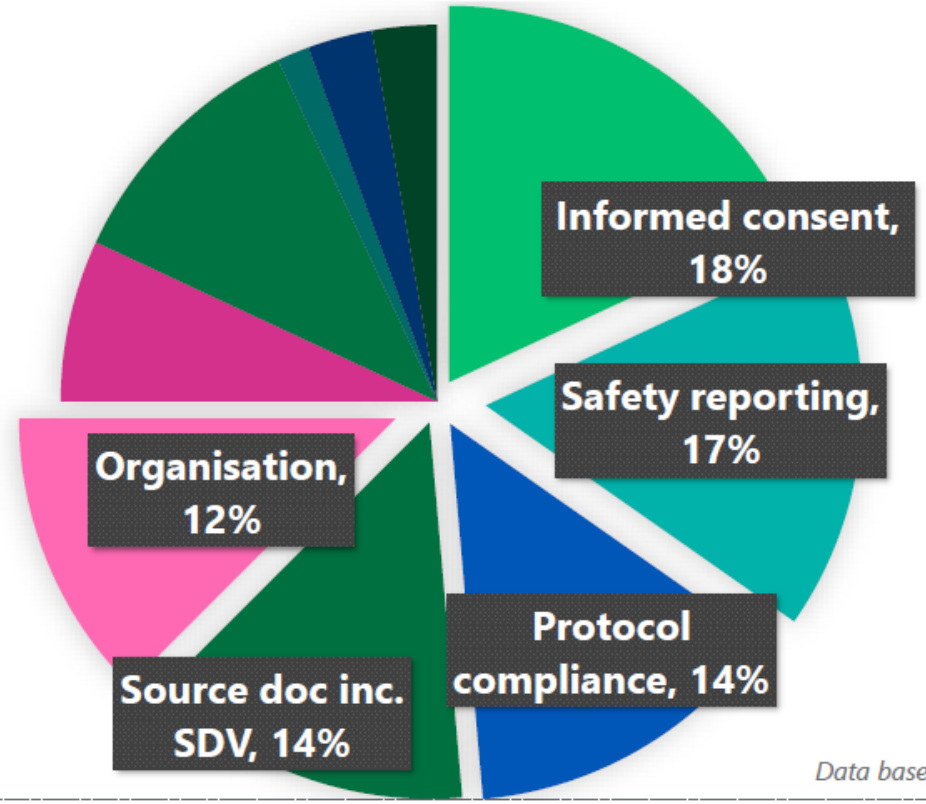

Data based on 19 closed investigator site inspections from 2016

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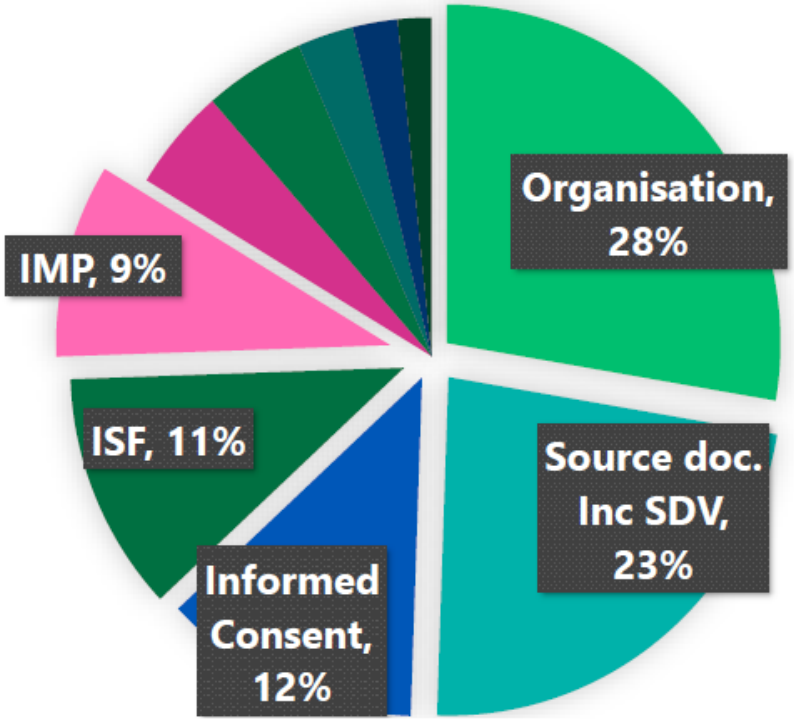
Findings By Area (Minor): Investigator Site Inspections



- Organisation
- Source doc. Inc SDV
- Informed Consent
- ISF
- IMP
- Safety Reporting
- Trial mgt, monitoring
- Protocol Compliance
- Reg/ethics
- Clincial sample mgt

Data based on 19 closed investigator site inspections from 2016

Deficiencies in Informed Consent

- **Incorrectly completed Informed Consents**
  - Boxes ticked instead of initialled
  - Missing subject/investigator/witness signatures
  - Missing dates of signatures
  - Investigator completed subjects name/date
  - Differences in dates of signature of investigator/subject/witness
- **Informed consent procedure not documented/adequately documented in source data**
- **Informed consent process as per protocol not consistent with Irish Law**

Deficiencies in Informed Consent

- **Incorrect procedure for consenting vulnerable subjects**
  - patients with dementia
  - language difficulties
  - unconscious patient
- **Deviations from the consent process documented in protocol/REC application form**
- **Use of only one witness instead of two according to SI 190**

Deficiencies in Safety Reporting

- Under-reporting of AEs/SAEs
- Adverse events inadequately documented in source data
- AEs/SAEs documented in source data but not in CRF and vice versa
- No start/stop dates of AEs/SAEs
- No causality assigned by investigators
- No evidence that investigator reviewed AEs
- No outcome documented
- SAE's not reported within required timelines
- Concomitant medication not documented

Deficiencies in Organisation

- **Delegation of Tasks**
  - Delegation Logs with no column for PI dated signature
  - Delegation Log not maintained on an ongoing basis
  - Missing details from Delegation Log i.e. signature, start and stop dates
  - Incorrect delegation of tasks i.e. research nurse delegated to perform tasks which should only be performed by an investigator

Deficiencies in Organisation

- **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

Deficiencies in Organisation

- **Inadequate systems in place for the management of training**
  - Training requirements not defined
  - 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

Deficiencies in Organisation

- **Management of SOP's**
  - SOPs not available for all tasks or incomplete
  - 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 completed and documented in good time

Deficiencies in Organisation

- **Document Control**
  - Current versions of documents not distributed and obsolete versions in use:
    - Protocols
    - Consent Forms
    - Patient Information Leaflets
    - Study Logs and Forms
    - SOP's

Deficiencies in Organisation

- **Investigator Site File Maintenance**
  - Essential Documents not filed in ISF
    - Ethics and Regulatory Approvals/Amendments
    - Clinical Trial Agreements
    - Trial Insurance
    - Current and Superseded Documents i.e. protocols/ICF
    - Completed Consent Forms
  - Screening and Subject ID Logs not up to date

Deficiencies in IMP Management

- Responsibility for IMP accountability not documented on the Delegation Log
- Incomplete accountability records
- Unused IMP was not accounted for and not retained at site

Deficiencies in IMP Management

- **Lack of awareness of the requirements**
  - Labelling
  - Storage requirements
  - Documentation
  - Randomisation
  - Dispensing
  - Returns
  - Destruction

Deficiencies in IMP Management

- **Temperature monitoring of IMP**
  - No temperature monitoring records for particular periods
  - Temperature records were not signed and dated
  - Minimum and maximum temperatures not recorded
  - Temperature excursions were noted …. No action taken (CAPA, quarantine)
  - No evidence of calibration of thermometers used for monitoring the storage temperature of the IMP at site and no evidence of awareness of the requirement for calibration
  - Deviations with randomisation process

Deficiencies in Source Data

- Unable to verify eligibility criteria
- Clinical significance for out of range lab values not documented on the lab reports
- Data corrections not as per GCP i.e. initials and data
- Patient identifiers visible on lab reports, ECGs etc
- Data in CRF does not match source data
- Unable to verify data in CRF from source data
- Unable to verify that study procedures have been performed

Possible actions arising from multiple major/critical deviations

- Deviations reviewed internally with representatives from Compliance, Human Products Authorisation and Registration and Human Products Monitoring soon after inspection
- Presentation made to HPRA Management Committee, Clinical Trial Sub Committee and Advisory Committee for Human Medicines, if necessary
- Recommendations regarding corrective actions/follow-up inspection
- Possible meeting with sponsor regarding corrective action plan
- Possible suspension of clinical trial activities

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Thank you

Questions?