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GCP and Data Integrity

Investigator Sites

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HPRA Information Day – GCP for IMP clinical trials

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Topics

- Data integrity and GCP
- Contribution of poor data integrity practices to common GCP findings at investigator sites
- Source documentation - systems & process considerations

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Data integrity & GCP

Data Integrity

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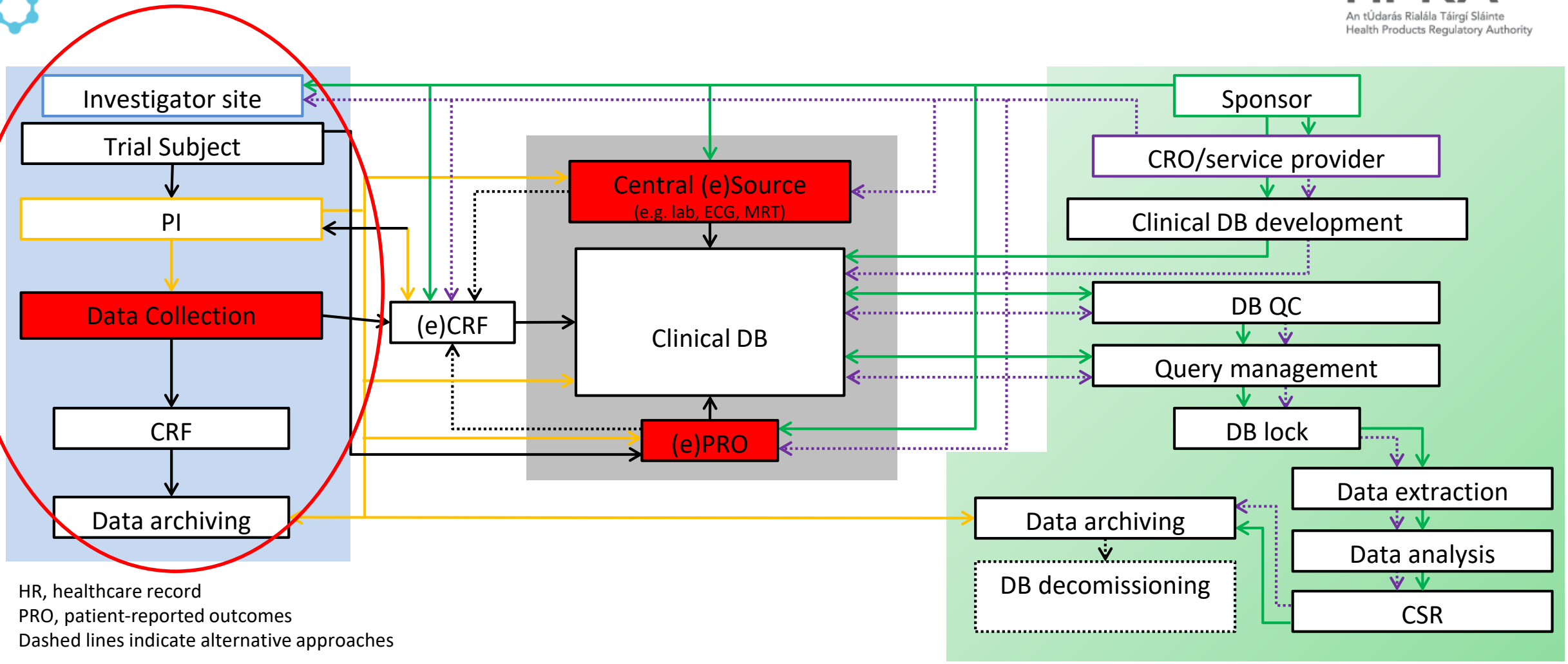
- What is data integrity? The extent to which all **data are complete, consistent and accurate throughout the data lifecycle**, from initial data generation and recording through processing (including transformation and migration), use, retention, archiving and retrieval. *Ref: EMA Data Integrity Q&A 2016 and MHRA GXP Data Integrity Guidance and Definitions, revision 1, 2018*
- How does data integrity apply to clinical trials? A key objective of GCP is to provide credible data.
- Outlined in ICH GCP E6 (R2), key principle 2:10 as:
    - *All clinical trial information should be recorded, handled, and stored in a way that allows its **accurate reporting, interpretation and verification.***
        - *Addendum: **This principle applies to all records referenced in this guideline, irrespective of the type of media used.***

Data Flow in Clinical Trials



HR, healthcare record
PRO, patient-reported outcomes
Dashed lines indicate alternative approaches

Source Data and Documentation

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ICH GCP 1.51: Source Data

'All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)'.

ICH GCP 1.52: Source Documents

'Original documents, data, and records *(e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments,* copies or transcriptions certified after verification as being accurate copies*, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)'.*

Source Data & Documentation

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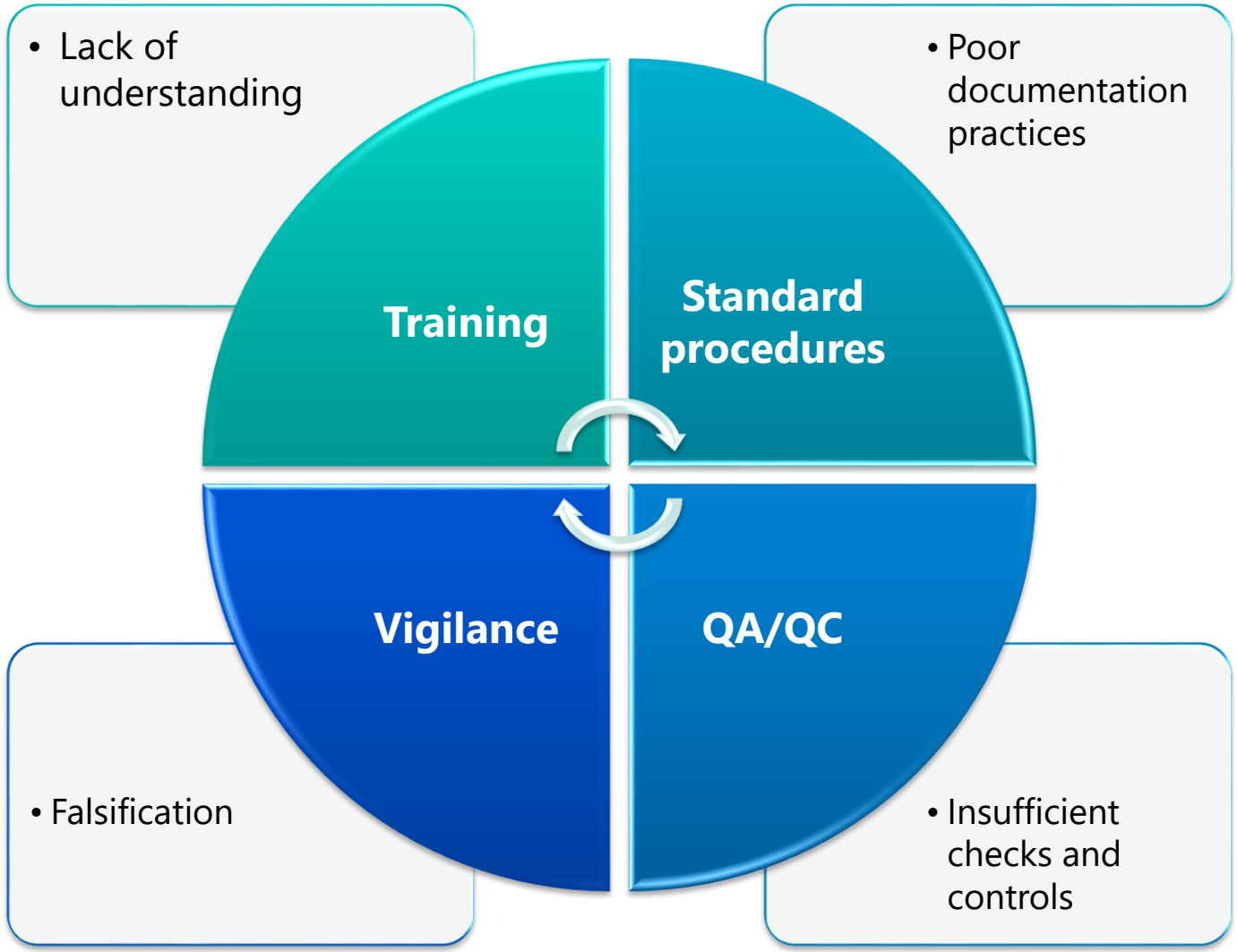
ICH GCP E6 (R2) 4.9 Records and Reports

- The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects.
- Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., *via* an audit trail).
- Source data should be attributable, legible, contemporaneous, original, accurate, and complete (ALCOAC)

Root Causes: Data integrity issues



The ALCOAC Principle – ICH GCP E6 (R2) 4.9.0

Attributable

Legible

Contemporaneous

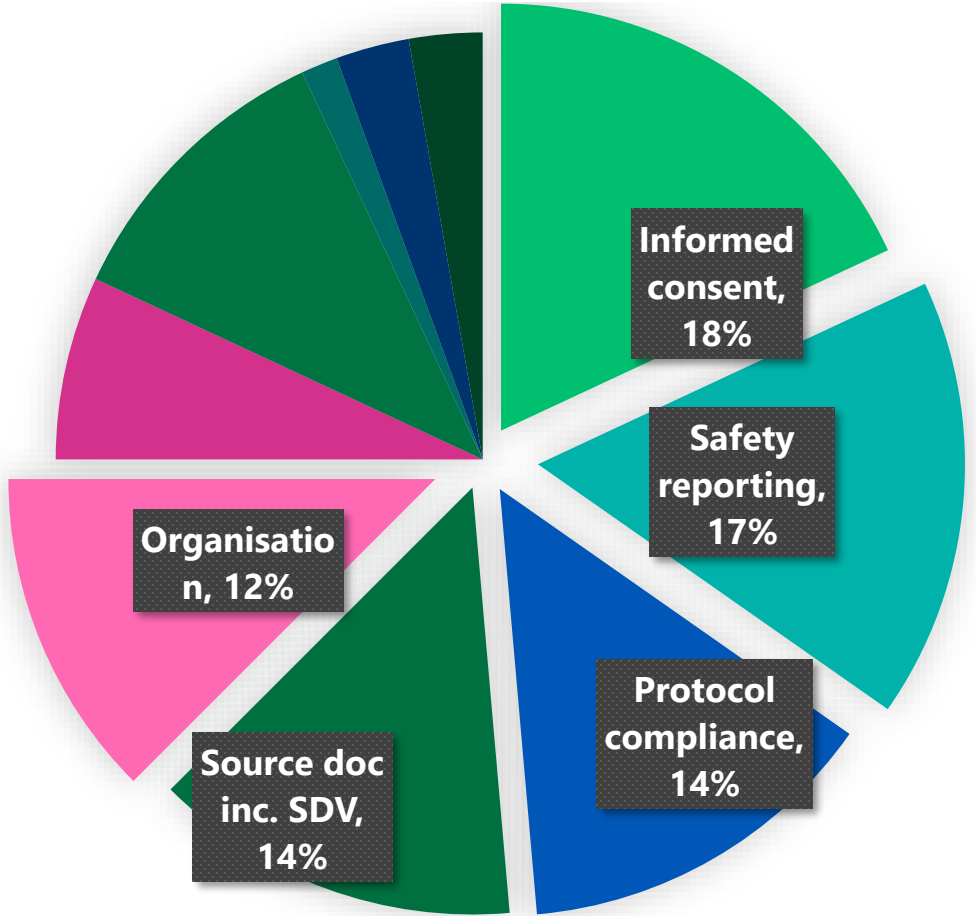
Original

Accurate

Complete

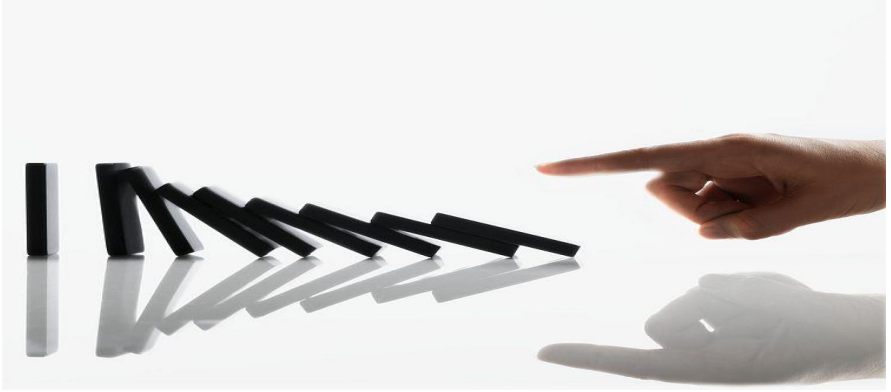
Common Findings: Investigator site inspections

Findings By Area (≥Major): Investigator Site Inspections



Common data integrity findings - Investigator site inspections

- Systems/process deficiencies: source documentation practices
- Impact of deficiencies in source documentation practices has impact on other areas:
  - Demonstrating compliance with rules for informed consent
  - Demonstrating compliance with protocol
  - Quality of safety reporting
  - Quality of case report forms



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Informed Consent

Key ref. ICH GCP E6 (R2) 2.9, 4.8.
S.I 190 of 2004, as amended Schedule 1

Informed Consent Form (ICF) completion

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Consent signature/date

e.g. subject signature dated by investigator, signatures completed in wrong sections

Consent form, check boxes

e.g. ticked instead of initialled, not fully completed, or not completed by subject

ICF Completion

Timing of consent

Unclear if the PIL/ICF was signed by the subject and Investigator together

Updates to forms

Corrections made to the ICF, not countersigned by subject

Documentation of the Process (Patient Information/Consent)

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Informed consent process

Details not documented (in full) in the medical chart, e.g. when information given, who involved in discussions, when consent taken

PIL/ICF copy

No entry to confirm PIL/ICF given to the subject, and GP informed, as applicable

IC process

Screening procedures

Timing of consent relative to screening procedures not clear from source records

Informed Consent Process: other common issues

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Change control

e.g. use of incorrect PIL/ICF version and/or late implementation

Re-consent

Participant not re-consented to the trial in a timely manner

Other types of deficiencies

Delegation

Participants consented by a Research Nurse and not an Investigator

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Protocol Compliance

Key ref. ICH GCP E6 (R2) 2.6 & SI 190 of 2004 Regulation 25

Selection & withdrawal of subjects

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Screening

Incomplete documentation for tests/assessment e.g. missing reports medical history, lack of clarity with regard to which results used for screening

Eligibility

Deficiencies in source records of the investigator's review and sign-off on inclusion/exclusion criteria, and final decision on eligibility

Selection to Withdrawal

Continuation/Withdrawal

Investigator decision that subject can continue IMP or requires a dose modification/withdrawal not recorded

Randomisation

Timing of randomisation unclear relative to eligibility decision (in particular when IXRS not used)

Treatment of subjects

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IMP treatment

Inconsistencies in treatment information recorded in medical chart/patient diary versus IMP accountability logs

Concomitant medication

Lack of documented checks for protocol prohibited/restricted medication

Concomitant medication

Record of checks e.g. no changes since last visit

Concomitant medication

Inconsistencies between source notes versus prescriptions versus CRF

Assessment of efficacy/safety

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Efficacy endpoints

deficiencies in documentation e.g. Oncology trials, RECIST – use of routine qualitative imaging reports

AE identification

Records of assessment of subject reported AEs during visits, do not record whether abnormal results from tests/procedures are clinically significant or not.

Efficacy & Safety

AE follow up

Traceability of AEs from visit to visit not clearly recorded e.g. start and stop dates, changes in severity

AE assessment

e.g. Investigator assessment of AE not recorded, all attributes not documented (e.g. severity, causality, seriousness)

Reports to the sponsor: Case Report Form & SAEs

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CRF inconsistencies

Data reported in CRF but not documented in source or inconsistent with source

SAE date of awareness

Not (clearly) recorded, therefore, adherence to immediate reporting timeline cannot be verified

Reports to Sponsor

Follow up reports

Unclear if all relevant follow-up information reported

Investigator SAE review

Missing investigator sign off/evaluation of SAEs, in particular when reported via electronic CRF

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Source Documentation

Systems, Processes & Practices

Traceability and Identification of Source data

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Key Requirement:

- ICH GCP E6 (R2) 8, Essential documents: The sponsor and investigator/institution should ***maintain a record of the location(s) of their respective essential documents including source documents***

Common/significant deficiencies:

- Data recorded in multiple locations/Not defined
- All source data not traceable (e.g. x-rays, medical history, clinical progress notes)

Expectations:

- The source data and their respective capture methods should be clearly defined
- One source defined at any time for any data element.
- Source data location list/agreement (version controlled)
- Maintain under change control

Documentation practices: Paper records

Key requirements: GCP 2.10, 2.13, 4.9, 8 & ALCOAC

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Common/significant deficiencies

- Clinical progress notes not compliant with ALCOAC
- Failure to consider need for specific documentation practice for trial (e.g. RECIST templates for oncology trials, AE/conmed logs)
- Worksheets not version controlled, quality controlled & subject to quality system provisions
- Templates/worksheets: not clear who has completed what sections
- Stickers/labels (potentially) covering entries/details
- Corrections were made to source records, which were not in line with GCP
- **Retrospective entries backdated**

Documentation practices: paper records
Key requirements: GCP 2.10, 2.13, 4.9, 8 & ALCOAC

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Expectations

- **Source documents:** capturing clinical trial data must be *'fit for purpose'* and ensure compliance with ALCOAC. Consider during planning stage
- **Worksheets:** if used, should be version controlled, quality controlled & subject to quality system provisions
- **AE/conmed logs:** Consider use for trials with expected large volume of data
- **Training:** Ensure staff are educated on ALCOAC & documentation practices for clinical trials
- **Changes/ Corrections:** dated, initialled, and explained. Should not obscure the original entry.
- **Retrospective notes:** agreed practice for entering retrospective notes in source documents. Clear policy of no back dating.

Documentation practices: Electronic records

Key requirements: GCP 2.10, 2.13, 4.9, 8 & ALCOAC

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Common/significant deficiencies

- Direct access
- System not validated to GCP specifications (ALCOAC + GCP 4.9)
- Copies of original records scanned, destroyed but not certified
- Archive: process not managed to take account of possible future software/ media changes

Documentation practices: Electronic records

Key requirements: GCP 2.10, 2.13, 4.9, 8 & ALCOAC

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Expectations

- **HPRA Website: Special topic on eHRs**
  http://www.hpra.ie/homepage/medicines/regulatory-information/clinical-trials/topics-of-special-interest/electronic-health-records-(ehrs)

- Physical security
- System to flag clinical trial subjects and search for trial records within the eHR
- Record of roles and access rights
- Direct and restricted access
- Medical oversight
- Data Processing & maintenance of data integrity
- Data protection
- Back-up of systems
- Certified copies

A final note…

''If it's not documented……

it's not done'.

'Document what is done……as well as,

what is not done!'

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Thank You