

The logo consists of the letters 'QRCC' in a bold, dark blue, sans-serif font, enclosed within a light blue rounded rectangular box with a thin dark border.

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Data Integrity – a Project Manager’s Perspective

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Lucielle Mansfield
Senior Clinical Project Manager
QRC Consultants Ltd

Content

- Text within this presentation is taken from the 'MHRA GXP Data Integrity Guidance and Definitions March 2018' verbatim /with small number of changes for the purpose of clarification.
- Individual references to the MHRA document have not been added.

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Agenda

- Background
- GCP Requirements and DI non-compliance
- MHRA GXP Data Integrity Guidance and Definitions
- Definition of Data Integrity
- What are data?
- The principles of ALCOA/ALCOA+
- What is a data life cycle
- DI risk assessment
- Examples of MHRA DI critical findings



Background

- One of the people who needs to comply!
- Managed clinical studies from protocol design to clinical study report, reporting and archive. Led risk management meetings.
- Interest in data integrity:
 - Pilot study for eTMF, became a TMF subject matter expert
 - Involved in TMF audit and mock inspection for which there were Data Integrity related findings.
 - Part of the team discussing DI governance/policy.

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GCP Requirements and non-compliance (1)

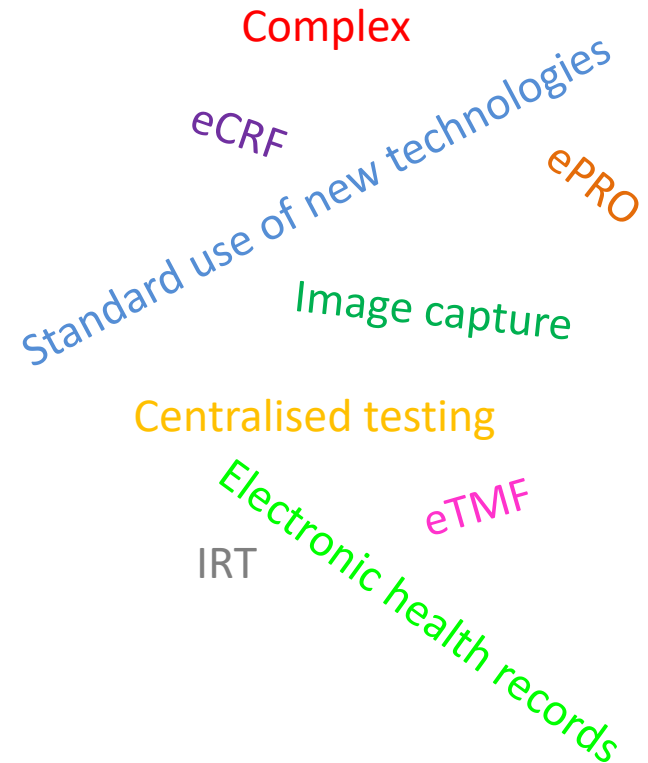
- According to ICH-GCP E6 (R2) 5.5.3 (h) when using electronic data...systems the **sponsor should ensure the integrity of the data** including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.¹

1, ICH-GCP E6 (R2) Nov 2016



GCP Requirements and non-compliance (2)

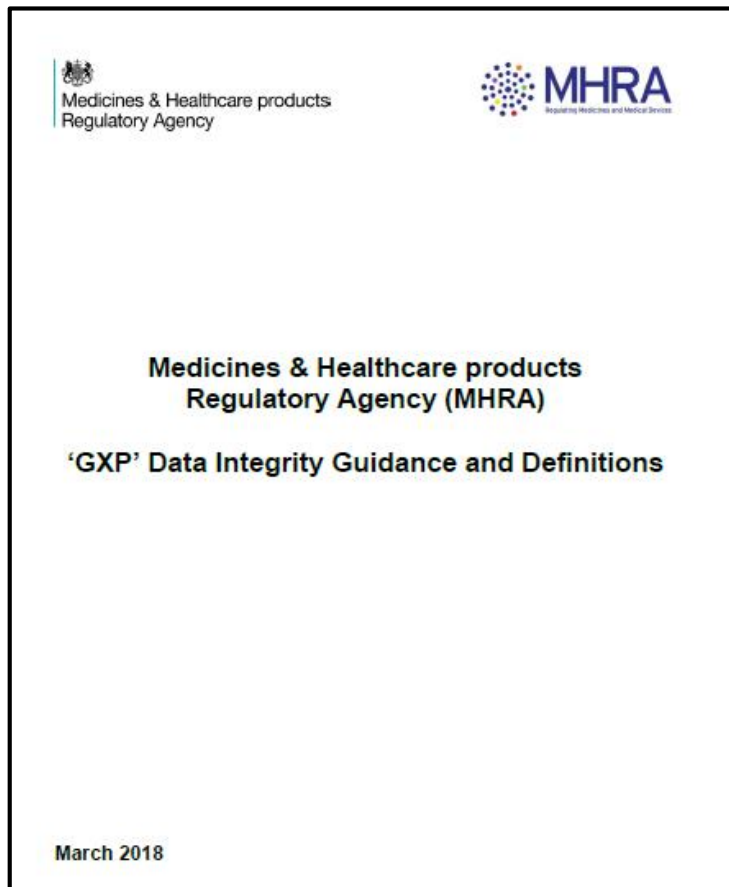
- There have been...”**fundamental failures** *(of DI)* **identified** by MHRA and international regulatory partners **during** GLP, GCP, GMP and GDP **inspections; many of which have resulted in regulatory action.**”



MHRA Publications/Guidance on GxP Data Integrity 09 March 2018

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MHRA GXP Data Integrity Guidance and Definitions (1)



- Details the MHRA's position on data integrity and the minimum expectation to achieve compliance.

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MHRA GXP Data Integrity Guidance and Definitions (2)

- DI Policy and DI built into quality management system and processes /working instructions; periodic audit.
- Training and awareness of DI (*by staff at all levels within the company, by the companies suppliers and it's distributors¹*)
- **Abide by the ALCOA/ALCOA+ principles**
- **DI risk assessments.**

1, EMA GMP Q+A DI Aug 2016

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Definition of Data Integrity

- Degree to which data are **complete, consistent, accurate, trustworthy, reliable** and that these characteristics of the data are maintained throughout the **data life cycle**.
- Applies to paper and electronic systems.

What are Data?

- **Facts, figures and statistics** collected together for reference or analysis. All **original records** and **true copies** of original records, including **source data** and **metadata** and all subsequent **transformations** and **reports** of these data, that are generated or recorded at the time of the GXP activity and **allow full** and complete **reconstruction** and **evaluation** of the GXP activity.

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Source / Raw Data (1)

- Definition: the original record (data) / the first-capture (paper or electronic) of information.
- Examples:
 - Measurements e.g. blood pressure
 - Medical history, physical exam information, clinical laboratory results
 - Imaging results (e.g. magnetic resonance imaging [MRI])
 - Self-reported data (e.g. symptoms, quality of life) .

<https://www.ncbi.nlm.nih.gov/books/NBK286004/>

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Source/Raw Data (2)

- Examples continued:
 - Derived or calculated from raw data e.g. BMI.
 - Interpreted according to pre-defined rules in the protocol e.g. assessments by clinical study staff or safety committees.
- Documented in a Source Data Agreement (SDA).
 - Issue: TMF audit finding – CRO SDA did not list the source data. Do not assume that the CRO understands the requirements.

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Source/Raw Data (3)

- Information that is originally captured in a dynamic state (electronically) should remain available in that state
 - Paper copies are not ‘raw data’
 - Exception: basic electronic equipment (e.g. balances) that does not store electronic data/provides only a printed data output then the printout constitutes the raw data.

Metadata

- Definition: Data that describe the attributes of other data and provide context and meaning.
- Permit data to be attributable to an individual (or if automatically generated, to the original data source).

Example of Metadata - Paper

- Trial subject A123, sample ref X789 taken 30/06/14 at 1456hrs. **3.5mg.**
Analyst: J Smith 01/Jul/14



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Electronic Metadata - Audit Trail

- Facilitates the reconstruction of the history of...events relating to the record...including the “who, what, when and why” of the action.

Audit Trail Considerations (1)

- Show changes to, or deletion of data while retaining previous and original data.*
- It should be possible to associate all data and changes to data with the persons making those changes, and changes should be dated and time stamped (time and time zone where applicable).
- The reason for any change, should also be recorded.
- The items included in the audit trail should...permit reconstruction of the process or activity.



Audit Trail Considerations (2)

- Audit trails (identified by risk assessment as required) should be switched on.
- Users should not be able to amend or switch off the audit trail.
- Where a system administrator amends, or switches off the audit trail a record of that action should be retained.
- It is not necessary for audit trail review to include every system activity (e.g. user log on/off, keystrokes etc.).

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Examples of Audit Trail Issues (1)

- No SDV audit trail for an eCRF
 - SDV check box was ticked when SDV was completed
 - Post-eCRF Go-Live amendment knocked off the SDV checked for data points on two separate forms
 - DM confirmed that the system “does not contain information about SDV to my knowledge”.

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Examples of Audit Trail Issues (2)

- SAEs reported via eCRF:
 - Couldn't demonstrate sign-off of SAEs by the PI, since this was via a system level signature not saved with the SAE CRF page. The audit trail only captured nurse confirming completion of the page and not PI sign-off.
 - Issue with regards to the time zone - PV provider, CRF vendor and PI all located in different time zones – email alert times difficult to determine.
 - No evidence of medical oversight in the PI's copy of the eCRF since audit trail only partial and did not contain dialogue (full audit trail saved at system level only).

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The Principles of ALCOA+

Attributable

Legible

Contemporaneous

Original

Accurate

Complete

Consistent

Enduring

Available

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Attributable

| Paper Records | Electronic Records |
|--|---|
| <ul style="list-style-type: none">• Full handwritten signature (and position, where applicable)• Date and, when necessary, time | <ul style="list-style-type: none">• Unique user logons that link the user to actions that create, modify or delete data• Unique electronic signatures• An audit trail that should capture user identification (ID) and date and time stamps |

WHO Annex 5 Guidance on Good Data and Record Management Practices, 2016

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Electronic Signatures

- The use of electronic signatures should be **compliant with** the requirements of **international standards** (eIDAS (EU); 21 CFR Part 11 (US FDA)) e.g. DocuSign.
- An inserted image of a signature or a footnote indicating that the document has been electronically signed (where this has been entered by a means other than the validated electronic signature process) is not adequate for GCP purposes.
- For further information refer to MHRA DI Guidance and Definitions 2018.

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Legible (traceable & permanent)

| Paper Records | Electronic Records |
|--|---|
| <ul style="list-style-type: none">• Use of permanent, indelible ink• No use of opaque correction fluid• Use of single-line cross-outs to record changes with name, date and reason recorded (i.e. the paper equivalent to the audit trail)• Archival of paper records by independent, designated personnel (archivist) in secure and controlled paper archives• Preservation of paper/ink that fades over time where their use is unavoidable. | <ul style="list-style-type: none">• Enforce the saving of electronic data at the time of the activity and before proceeding to the next step of the sequence of events• Use of secure, time-stamped audit trails that independently record operator actions and attribute actions to the logged-on individual• Restrict access to enhanced security permissions such as the system administrator role• Disable and prohibit the ability to overwrite data• Validated backup of electronic records to ensure disaster recovery |

WHO ANNEX 5

WHO Annex 5 Guidance on Good Data and Record Management Practices, 2016

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Contemporaneous

| Paper | Electronic |
|--|--|
| <ul style="list-style-type: none">• Written procedures, training, review and audit/self-inspection controls that ensure personnel record data entries and information at the time of the activity directly in official controlled documents | <ul style="list-style-type: none">• Ensure that data recorded in temporary memory are committed to durable media upon completion of the step or event and before proceeding to the next step or event in order to ensure the permanent recording of the step or event at the time it is conducted• Data entry should be automatically date and time stamped• Availability of the system to the user at the time of the activity.• Controls that allow for the determination of the timing of one activity relative to another (e.g. time zone controls) |

WHO Annex 5 Guidance on Good Data and Record Management Practices, 2016



Original Record

- The first or source capture of data or information e.g. original paper record of manual observation or electronic raw data file from a computerised system...
- Original records can be Static (e.g. paper/pdf) or Dynamic (e.g. Excel files and SAS datasets).

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Original Record – DI Risk

- Data integrity **risks** may occur when people choose to rely solely upon **paper printouts or PDF reports** from computerized systems without meeting applicable regulatory expectations for original records. Original records should be reviewed – this includes electronic records. **If the reviewer only reviews the subset of data provided as a printout or PDF, risks may go undetected and harm may occur.**

WHO Annex 5 Guidance on Good Data and Record Management Practices, 2016

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True Copy

- Definition: A **copy** (irrespective of the type of media used) of the original record that has been **verified** (i.e. by a **dated signature** or by generation through a **validated process**) to have the same information, including data that describe the context, content, and structure, as the original.
- Example: Print results of GMC status of PI from GMC website sign and date.
- Validated process: refer to “Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic) 06 December 2018 for true “certified copies”.

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Accurate

- Controls that assure the accuracy of data in paper records and electronic records include, but are not limited to:
 - Qualification, **calibration and maintenance** of equipment, such as **balances** and pH meters, that generate printouts
 - **Validation of computerized systems** that generate, process, maintain, distribute or archive electronic records
 - Systems must be **validated** to ensure their integrity **while transmitting between/among computerized systems** (*data transfer/migration*)
 - **Validation of analytical methods** (*e.g. Phase 1 - PK blood/urine samples*)
 - Investigation of deviations and **doubtful** and out-of-specifications **results** etc (*via data review*).

WHO Annex 5 Guidance on Good Data and Record Management Practices, 2016

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Accurate - Example

- “Investigation of deviations and doubtful and out-of-specifications results”: CTMS system was used to review/monitor data in real time
- Data outlier identified:
 - Patient questionnaire
 - 100% data was completed and completed on time.
 - Data from other subjects from other sites was variable and subjects were typically ~50-60% compliant
 - Investigator was falsifying subject data.

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ALCOA+

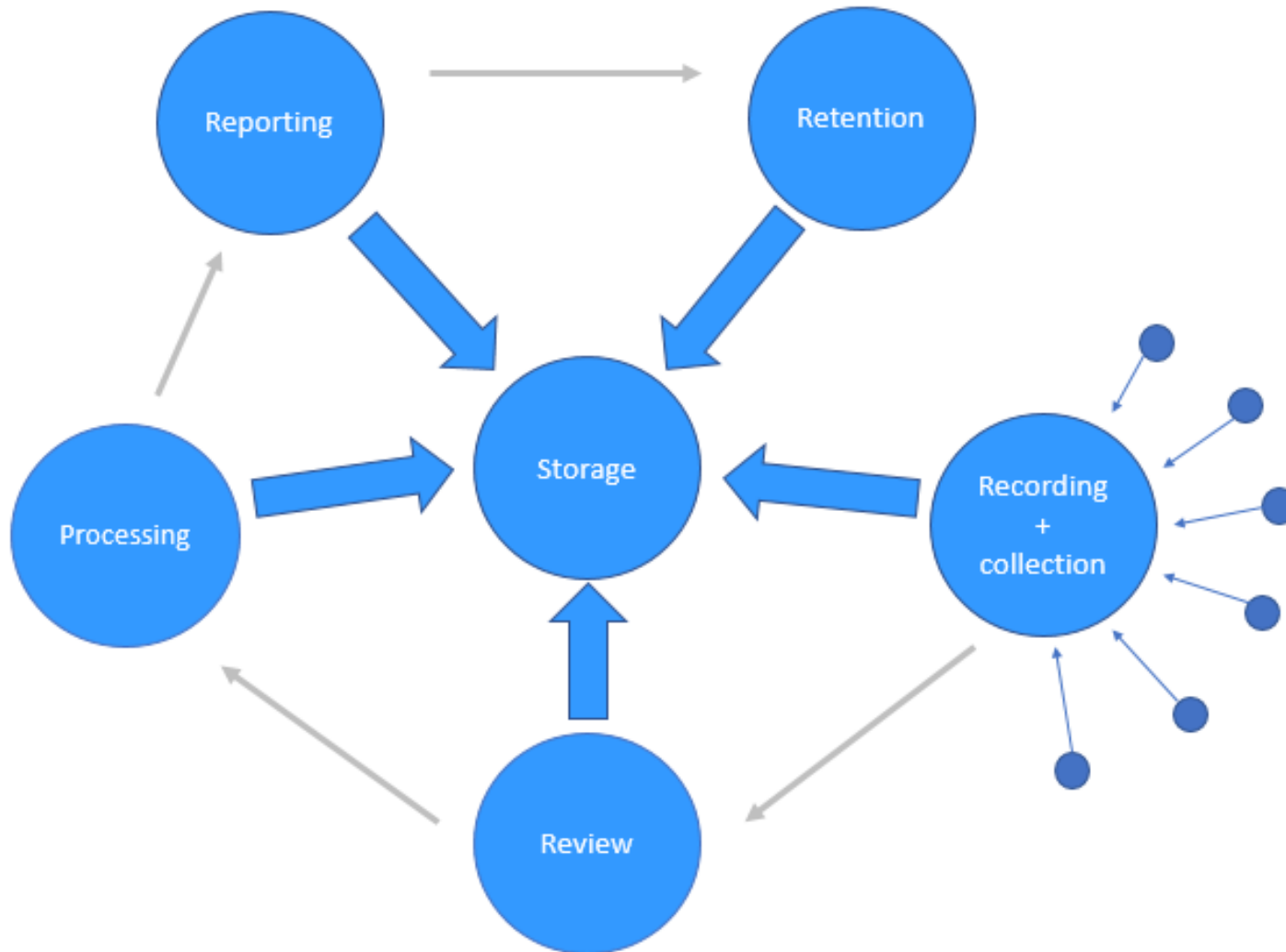
- Complete – the data must be whole; a complete set
- Consistent - the data must be self-consistent
- Enduring – durable; lasting throughout the data lifecycle
- Available – readily available for review or inspection purposes.

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What is a Data Lifecycle?

- All phases in the life of the data from generation and recording through processing (including analysis, transformation or migration), use, data retention, archive/retrieval and (where appropriate) destruction.

What is a Data Lifecycle?



Recording and Collection of Data

- Organisations should have an appropriate level of process understanding and technical knowledge of systems used for data collection and recording, including their capabilities, limitations and vulnerabilities.
- The selected method (*of data collection*) should ensure that data of appropriate accuracy, completeness, content and meaning are collected and retained for use.

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Data Transfer

- The process of **transferring data** and **metadata** between different data storage types, formats, or computerised systems.

Data Transfer - Considerations

- **Procedures** should include a rationale, and be robustly designed and **validated** to ensure that data integrity is maintained during the data lifecycle.
- **Careful consideration** should be given to understanding **the data format and the potential for alteration** at each stage of data generation, transfer and subsequent storage.
- There should be an **audit trail** for the data transfer process.

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Data Transfer - Examples

- Integration into the clinical database:
 - IRT IMP data
 - PK data
 - Safety lab data
- Transfer of data from the clinical database to the safety database for SAEs
- Transfer specifications document (if routine this may be captured in SOPs)
- Test transfers including documentation thereof.

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Data Review

- The approach to reviewing specific record content, such as critical data and metadata, cross-outs (paper records) and audit trails (electronic records) should meet all applicable regulatory requirements and be risk-based.

Data Review - Considerations

- There should be a **procedure** that **describes** the **process for review and approval of data**.
- A procedure should **describe** the **actions** to be taken if data review identifies an error or omission.
- This procedure should enable data corrections or clarifications to provide **visibility** of the original record, and traceability of the correction, using ALCOA principles
- Data review should be **documented**.

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Data Review - Examples

- Automated checks:
 - To detect data that are illogical, unexpected, missing, redundant, or are outside of defined study parameters; usually implemented via programming logic (pre-defined in edit check plan/ data validation specifications)¹
- Manual:
 - Monitoring (SDV) (Monitoring Plan)
 - Pre-defined/agreed checks completed by data managers/staff (DMP/DVP)
 - Sponsor data review (0%, 10%, 50% and 100% of data captured) (DMP/DVP)
 - Database reconciliation (during the study, or end (if applicable/justified)) (DMP)

1, DIA TMF Reference Model Index v3.1.0

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Data Review - Excluding Data

- Data may only be excluded where it can be demonstrated through valid scientific justification that the data are not representative of the quantity measured, sampled or acquired.
- Example: PK data outlier data that is proven as a result of error in sample analysis. N.B. strict/controlled written procedures at the Bioanalytical lab and PK group and if data is excluded it is documented in the Bioanalytical Report.

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Data Processing

- **Definition:** A sequence of operations performed on data to extract, present or obtain information in a defined format
- **Considerations:**
 - **Traceability** including who performed the activity.
 - **Audit trails** and record retention to allow reconstruction of the processing activities.
- **Example:** Data transformed (by statistical programming (SDTM)) into analyzable data sets i.e. TLGs

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Data Retention

- Data retention may be for **archiving** (protected data for long-term storage) or **back-up** (data for the purposes of disaster recovery).
- Arrangements should ensure the **protection of records** from deliberate or inadvertent **alteration** or **loss** (and protected against any **accidental damage** such as fire or pest with regards to archiving).
- Example: IRT portable hard drive of data.

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Data Migration

- Definition: The process of moving **stored data** from one durable storage location to another.
- If necessary, change the format of data to make it usable or visible on an alternative computerised system.
- Example: CRO eTMF to Sponsor eTMF

Archive

- Archive arrangements must be designed to permit **recovery** and **readability** of the **data** and **metadata** throughout the required **retention period**.
- Electronic data...process should be **validated**, and in the case of **legacy systems** the ability to **review data** **periodically** verified (i.e. to confirm the continued support of legacy computerised systems).

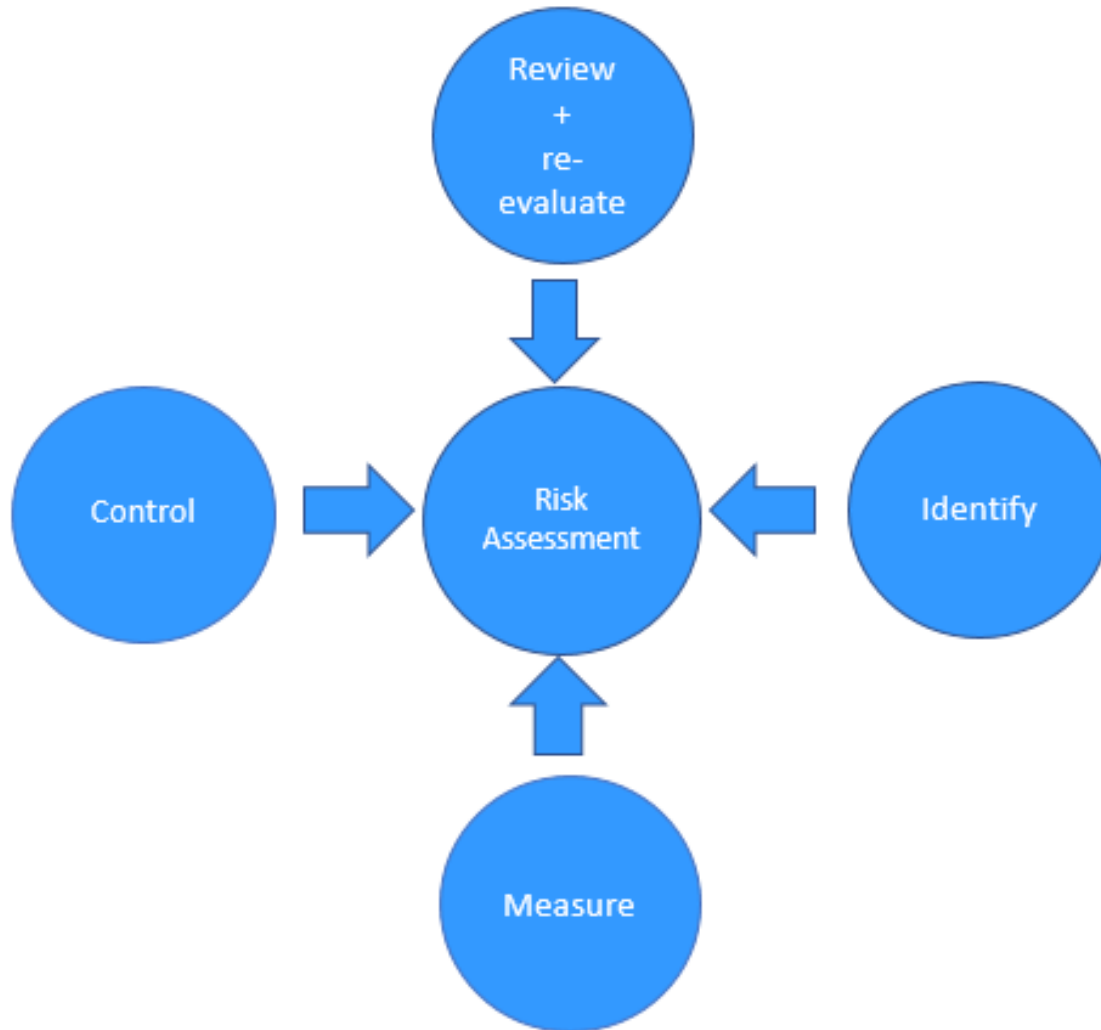


DI Risk Assessment (1)

- *(The MHRA DI)* guidance aims to promote a risk-based approach to data management that includes data risk, criticality and lifecycle. Users of this guidance need to understand their data processes (as a lifecycle) to identify data with the greatest GXP impact. From that, the identification of the most effective and efficient risk-based control and review of the data can be determined and implemented.

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DI Risk Assessment (2)



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Identify Risks

- Determined by the potential to be deleted, amended or excluded without authorisation and the opportunity for detection of those activities and events.
- The way in which data are generated will influence the **inherent** data integrity **risk**.
 - Higher risk: a complex, inconsistent process with open-ended and subjective outcomes
 - Lower risk: a simple task that are undertaken consistently, are well defined and have a clear objective.

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Measure Risk - Assign Criticality

- Data has varying importance to quality, safety and efficacy decisions.
- Data criticality may be determined by considering **how the data are used** to influence the decisions made.
- Example: data for a primary endpoint vs exploratory.

Risk Mitigation/Control

- Design systems (and processes) to ensure DI.
- Computerized systems with electronic data should be validated for their intended use and the potential of the system to affect human subject protection and reliability of trial results.
- On-going validation due to system changes/changes to the protocol.
- For further guidance regarding level of validation/qualification refer to: EMA Q&A GCP Matters Q9.

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Risk Mitigation/Control - Validation

- According to ICH E6 R2 5.5.3.a, the sponsor should ensure and document that the electronic data processing system(s) conforms to the sponsors established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

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Validation Example - UAT

- Trial-specific user acceptance testing e.g. IRT, eCRF, ePRO etc. Example given below is IRT.
 - Did the system change (i.e. upgrade) since the last study?
 - (Review and approval of user requirement specifications including compliance with the protocol/ intended use)
 - Carried out by Sponsor and CRO. Clinical Operations and Clinical Supplies.
 - IRT SOP and UAT scripts.
 - Use the user manuals; Make mistakes; Check the audit trail of critical steps; Check reports; Print outs; Check unblinding process; Check linked processes e.g. IMP supplier.
 - 2-3 days testing.
 - Document. Re-test and document.
 - Approval documents retained in the TMF.
 - Completed UAT scripts were retained as supporting documentation.

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Examples of MHRA DI critical findings (1)

Accuracy and quality of the data from questionnaires could not be confirmed:

- Completed for eligibility and primary endpoint data
- Contained language /medical terms not easily understood by patients
- Should have been completed by a health care professional.
- There was no clear instruction or training provided to sites on how these should be completed.
- It could not be confirmed that a Health Care professional/delegated investigator staff member had completed or overseen the questionnaire completion.

MHRA DI critical findings -Commercial Sponsor
GCP INSPECTORATE, GCP INSPECTIONS METRICS REPORT, METRICS PERIOD:
1st April 2016 to 31st March 2017

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Examples of MHRA DI critical findings (2)

Electronic Health Records (eHRs) and the paper source data used on the trial had significant deficiencies:

- It was not possible to verify:
 - Who completed them
 - When they were completed
 - Who had been making changes and why.
- Entries could be deleted and amended.
- The audit trail provided for the eHR did not show if the entries were new, deletions or amendments.
- Due to these deficiencies integrity of the data could not be confirmed.

MHRA DI critical findings – Commercial Sponsor (Site inspection)
GCP INSPECTORATE, GCP INSPECTIONS METRICS REPORT, METRICS PERIOD: 1st April 2016 to
31st March 2017



Examples of MHRA DI critical findings (3)

- **Inability to adequately confirm** that the **database changes to the data had all been authorised** by the investigator prior to the change being made. This was due to the process of resolving queries by email.
- Loss of control of the source data by the investigator in the database (Investigator entered some source data into the database) and **complete absence of key source data at the site** (no trial diaries were retained upon advice of the CTU) **relating the endpoint of the trial.**
- **Inconsistencies between** the data at site on **paper CRF/Worksheet** and the **database** and whether data were complete (e.g. adverse events reported).

MHRA DI critical findings - University CTU – key issues. GCP INSPECTORATE, GCP INSPECTIONS METRICS REPORT, METRICS PERIOD: 1st April 2015 to 31st March 2016.

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Any questions?

