Session 4: Good Data Governance Practice Updates

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ICH E6 (R3) Draft – Good Data Governance Practices

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U.S. FOOD & DRUG ADMINISTRATION

Medicines & Healthcare products Regulatory Agency

Health Canada Santé Canada

Overview of this Session

- Discuss the risk proportionate approach to data governance
- Discuss the importance of good data governance practices in the conduct of a clinical trial
- Provide updates to ICH E6R3 related to data governance, including updates to sponsor and investigator responsibilities
- Provide case examples to illustrate the importance the new draft recommendations in E6R3 related to data governance

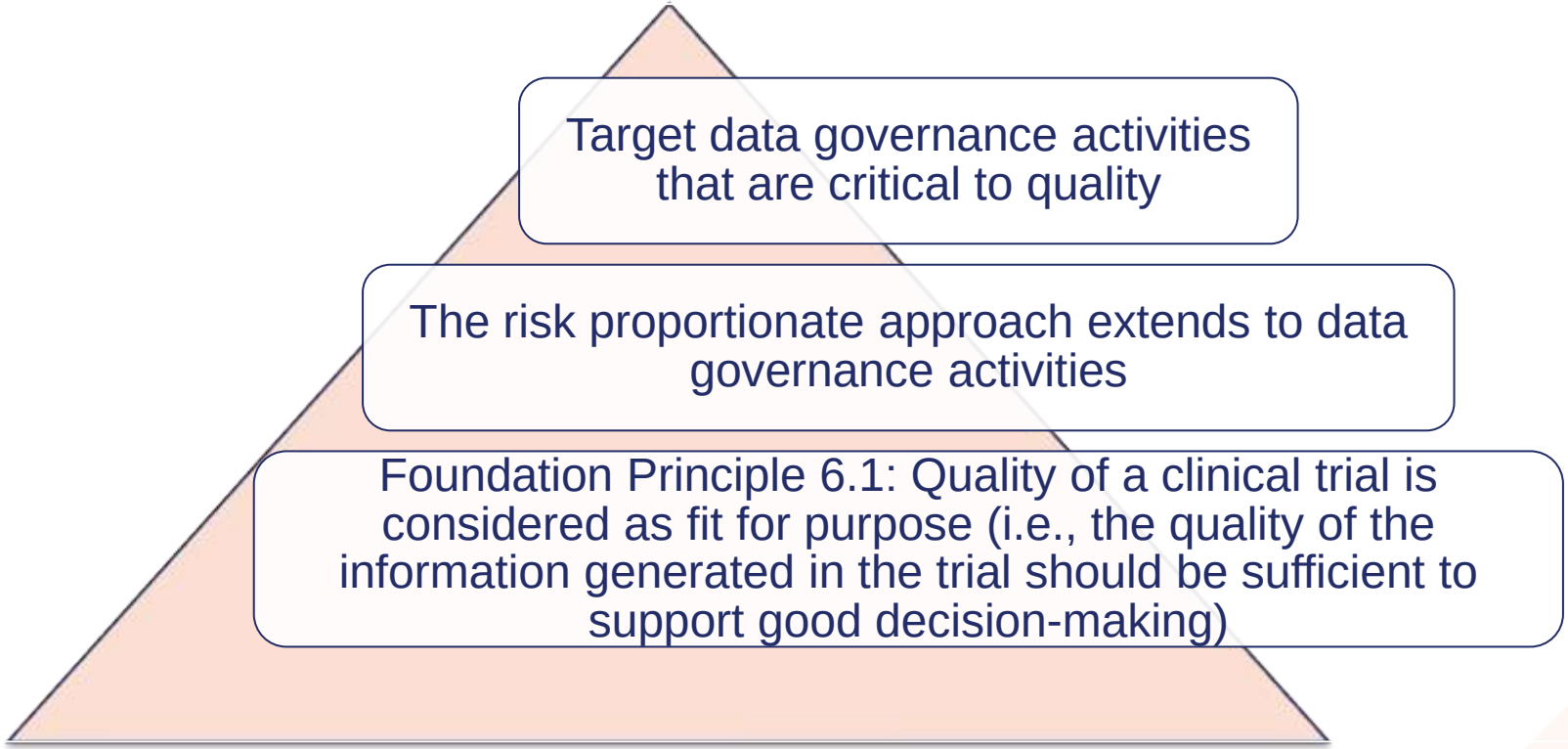
Disclaimer Slide

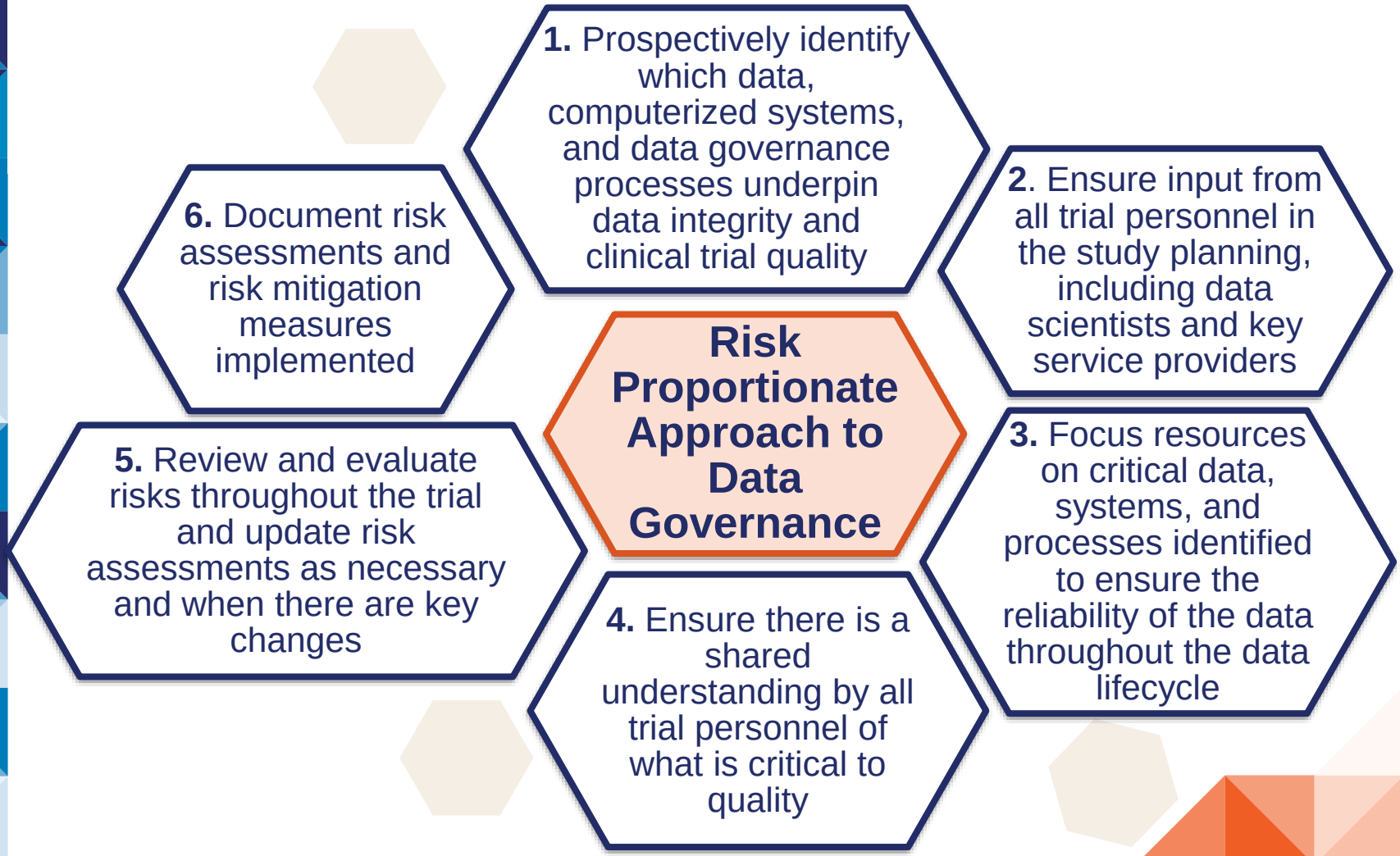
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

ICH E6 (R3) – Risk Proportionate Approach

Builds	• On key concepts outlined in ICH E8(R1) General Considerations for Clinical Studies
Highlights	• The importance of building quality into clinical trials and having leadership that promotes an open reporting culture, encourages investigation, and supports proportionate management of any critical errors
Includes	• Identifying, during study planning, factors that are critical to the quality to the trial and the management of risks to those factors during study conduct
Emphasizes	• That trial processes and risk mitigation strategies implemented should be proportionate to the importance of the trial data and the risks to trial participant safety and data reliability

ICH E6 (R3) - Risk Proportionate Approach to Data Governance




1. Prospectively identify which data, computerized systems, and data governance processes underpin data integrity and clinical trial quality
2. Ensure input from all trial personnel in the study planning, including data scientists and key service providers
3. Focus resources on critical data, systems, and processes identified to ensure the reliability of the data throughout the data lifecycle
4. Ensure there is a shared understanding by all trial personnel of what is critical to quality
5. Review and evaluate risks throughout the trial and update risk assessments as necessary and when there are key changes
6. Document risk assessments and risk mitigation measures implemented
Risk Proportionate Approach to Data Governance

Risk-Proportionate Approach Throughout the Data Lifecycle

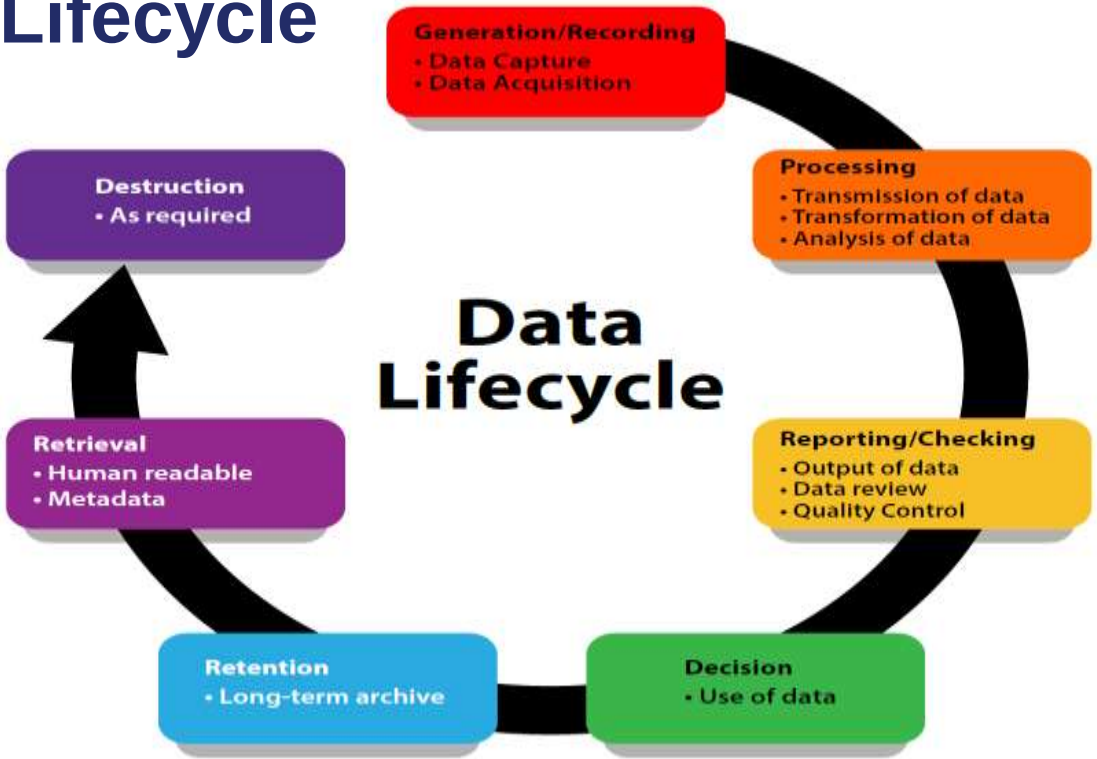
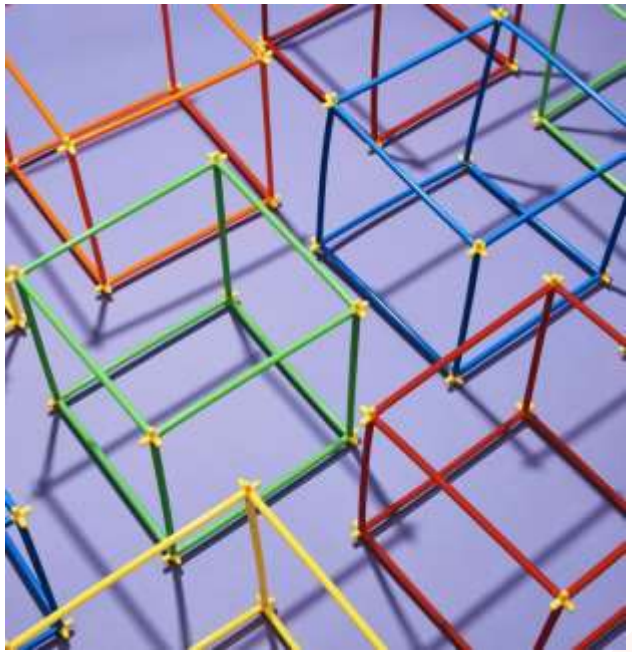


Figure taken from Khin, N.A. et al. Data integrity in global clinical trials: discussions from joint US Food and Drug Administration and UK Medicines and Healthcare Products Regulatory Agency Good Clinical Practice Workshop. Clin. Pharmacol. Ther. 108(5), 949– 963 (2020)

Overview

- Importance of data governance: ICH E6 (R3)
- 4 key processes for data life cycle
- Responsibilities of sponsor and investigator for management of data and records in computerized systems
- Requirements for validation of computerized systems
- Deficiencies observed for validation of computerized systems



ICH E6 (R3)- Data Governance

- Appropriate management of data integrity, traceability and security
- Reliable results from clinical trials
- Data handling, and record-keeping
- Risk-proportionate processes and fit-for-purpose system controls
- Relevant metadata and audit trails
- Structured data transfer and data migration approaches

Processes for Full Data Life Cycle

To ensure data protection of trial participants' confidential data

To ensure computerized systems are fit for purpose and used appropriately

To safeguard essential elements of the clinical trial, such as randomization, dose escalation and blinding

To support key decision making, such as data finalization prior to analysis, unblinding, allocation to analysis data sets, changes in clinical trial design

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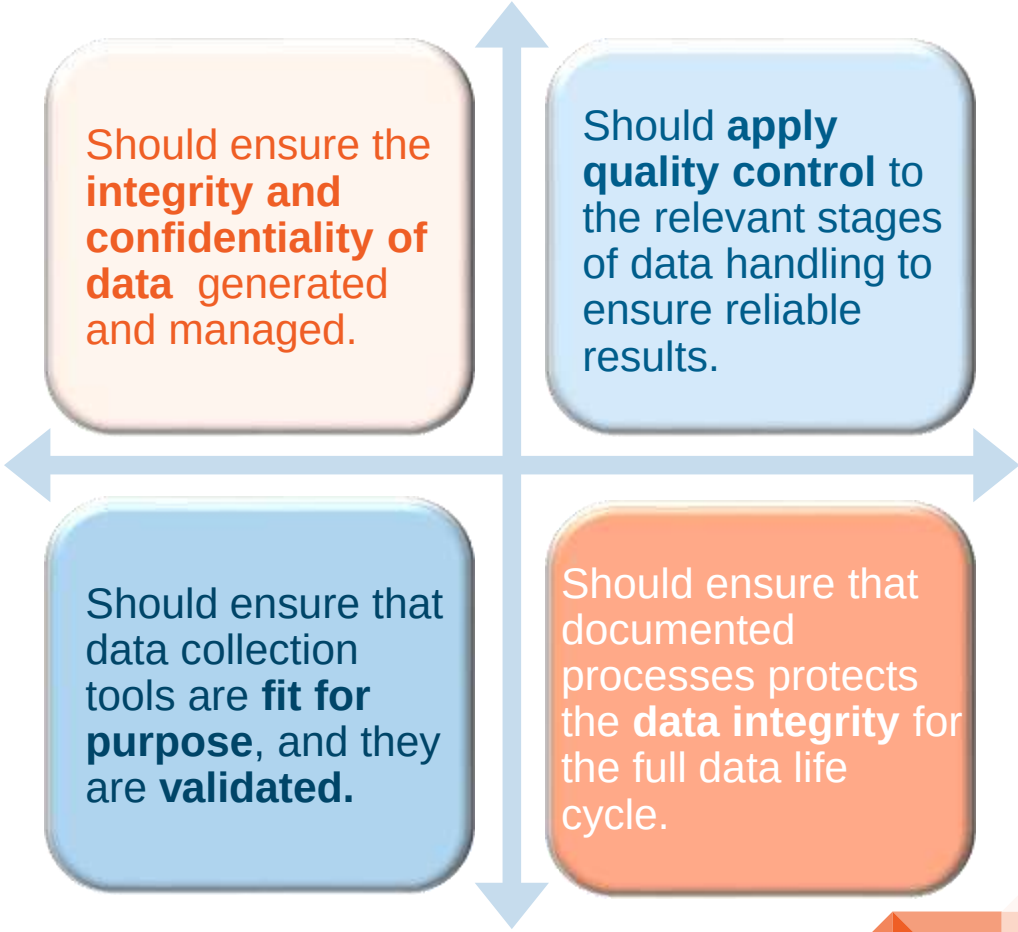
Investigator Responsibility for Records

In generating, recording and reporting trial data, the investigator should ensure the **integrity of data** under their responsibility, irrespective of the media used.

The investigator should ensure that **data systems** deployed by the sponsor are **used as specified per instructions**.

The investigator should ensure the **accuracy, completeness, legibility and timeliness of the data** reported to the sponsor in the data systems completed by the site.

Sponsor Responsibility for Data and Records



Sponsor Responsibility for Data and Records

When using computerized systems in a clinical trial, the sponsor should:

- Have a **record** of the computerized systems including the use, functionality, interfaces and the validation status.
- Ensure that the requirements for the systems deployed are implemented with **documented procedure and adequate training.**
- Assess and document whether systems deployed by the investigator are **fit for purpose** and the known issues can be appropriately **mitigated**.
- Ensure that there is a process in place for service providers and investigators to inform the sponsor of **system defects identified**.

Responsibilities for Computerized Systems

The sponsor is responsible for ensuring that for computerized systems which they deploy, the expectations are addressed in a **risk proportionate** manner.

The sponsor should review whether the systems used by the investigator/institution are **fit for purpose** in the context of the trial.

The responsible party should ensure that those developing computerized systems for clinical trials are aware of the **intended purpose** and the **regulatory requirements** that apply to them.

Principles of Data Management

COLLECT THE RIGHT DATA WITH THE RIGHT TOOLS

COLLECT COMPLETE AND ACCURATE DATA

APPLY APPROPRIATE CONTROLS

CLINICAL STUDY REPORT

Apply Appropriate Controls

- Procedures and Personnel Training
- Data Flow
  (Data Transfer/Import/Interfaces)
- Systems Controls
  (Security/**Validation**/Access Control)
- Quality Control of Data / Data Validation

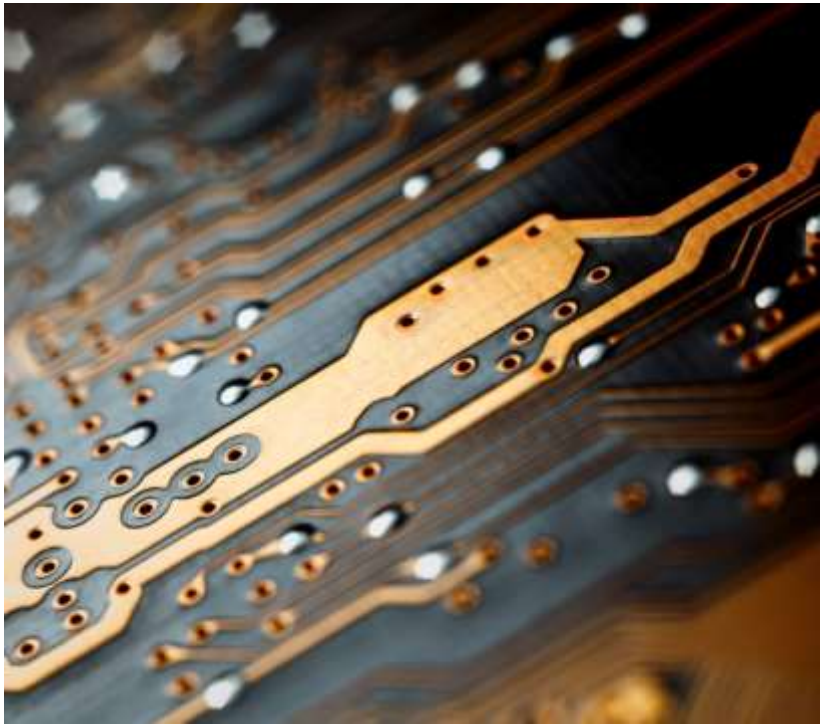
Validation Principles

Appropriate controls of the system are in place

Documentation exist to support the application of the controls

The system is fit for purpose

Validation of Computerized Systems



- The approach to validation of computerized systems should be based on a risk assessment that considers:
  - The intended use of the system;
  - The purpose and importance of the data/record that is collected/generated, maintained and retained in the system;
  - The potential of the system to affect the well-being, rights and safety of trial participants and the reliability of trial results.

System Failure and Technical Support

Contingency procedures should be in place to prevent loss or lack of accessibility to data essential to participant safety, trial decisions or trial outcomes.

There should be mechanisms (e.g., Help desk support) in place to document, evaluate and manage issues.

Defects and issues should be resolved according to their criticality. Issues with high criticality should be resolved in a timely manner.

Applying Risk Proportionality to Data Governance: Examples of Deficiencies on Computer System Validation

Validation of Databases

(Examples of Deficiencies)

- Was not adequately validated for its intended use;
- eCRF was not designed/validated to collect per protocol all primary efficacy endpoint data;

Impact: Data collected did not contain all the data variables needed to appropriately assess and analyze the primary endpoint of the study.

The approach to validation of computerized systems should be based on a risk assessment that considers the intended use of the system.

Validation should demonstrate that the system conforms to the established requirements for completeness, accuracy and reliability and is consistent with intended performance.

Validation of Databases (*cont'd*)

(Examples of Deficiencies)

- Lack of adequate documentation (system design, testing and change control procedures);

Impact: Incomplete evidence of validation

Procedures should cover the system design, validation, functionality testing, release, setup, installation and change control until decommissioning.

Systems should be appropriately validated prior to use with adequate change control procedures implemented.

Qualification and validation documentation should be maintained and retained.

Validation of Databases (*cont'd*)

(Examples of Deficiencies)

- The system Test Script execution records did not include testing of all requirements;
- The critical functionality testing of randomization in IRT system was not performed;

Impact: Participants were randomized incorrectly.

Validation should include defining the requirements and specifications for the system and their testing, along with the associated documentation to ensure the system is fit for purpose, especially for critical functionality.

Validation should demonstrate that the system conforms to the established requirements for completeness, accuracy and reliability and is consistent with intended performance.

Validation of Databases (*cont'd*)

(Examples of Deficiencies)

- Issues identified for design, and control;
- Missing AE page and incomplete information on SAE page;

Impact: Data quality for safety assessment.

Validation should demonstrate that the system conforms to the established requirements for completeness, accuracy and reliability and is consistent with intended performance.

Validation should include defining the requirements and specifications for the system and their testing, along with the associated documentation to ensure the system is fit for purpose, especially for critical functionality.

Validation of Databases (*cont'd*)

(Examples of Deficiencies)

- Audit trails were not complete to show all types of changes specifically the deletions;

*Impact: D*ata integrity

Systems are designed to permit data changes in such a way that the initial data entry and any subsequent changes or deletions are documented.

Validation should demonstrate that the system conforms to the established requirements for completeness, accuracy and reliability and is consistent with intended performance.

Critical to Quality Factors

- Design per intended use and according to the protocol.
- Data integrity principles should be applied during the system design.
- System should conform to the established requirements for completeness, accuracy and reliability.
- Functionality testing to be performed in general, and in particular for the critical functionality testing.
- Documented procedures in place for system design, validation and functionality testing, release, setup, installation and change control.

Processes for Full Data Life Cycle

To ensure data protection of trial participants' confidential data

For managing computerized systems to ensure that they are fit for purpose and used appropriately

To safeguard essential elements of the clinical trial, such as randomization, dose escalation and blinding

To support key decision making, such as data finalization prior to analysis, unblinding, allocation to analysis data sets, changes in clinical trial design

What does ICH E6 (R3) say about trial participant confidentiality?

Confidentiality: Prevention of disclosure to other than authorised individuals of a participant's identity or their confidential information

The confidentiality of information that could identify participants should be protected…

The informed consent discussion and the informed consent materials to be provided to participants should explain… that records identifying the participant will be kept confidential…

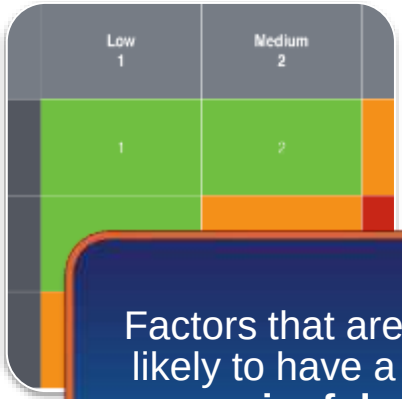
The sponsor should:

Ensure the… confidentiality of data generated and managed.

Implement appropriate measures to protect the privacy and confidentiality of personal information of trial participants….

Ensure that trial data are protected from unauthorised access

Confidentiality Breach is a Risk to Participant's Rights



Factors that are likely to have a **meaningful impact on participant's rights**

Risk control should be proportionate to the importance of the **risk to participants' rights**

The potential of the computerised system **to affect the rights of trial participants**

Applying Risk Proportionality to Data Governance: Case Example on Maintaining Participant Confidentiality

CRO Inspection Finding – Breach of Participant Confidentiality

Personally identifiable data was held in the eCRF/EDC (and its audit trail) for all trial patients. Sponsor/CRO users had EDC read access to these data.

Participant Informed Consent did not specifically give consent for this personally identifiable data to be shared in the EDC or with the Sponsor/CRO staff. Patients had only consented to data being 'pseudo-anonymised.'

The servers for the EDC were held outside of the UK. Consent only permitted **pseudo-anonymised data** to be transferred outside of the UK/EU.

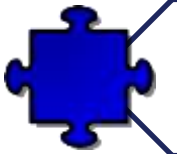
Neither the protocol nor any other particulars or documents accompanying the application to the MHRA or REC included information to state that personally identifiable data would be transferred and stored in the EDC .

What Data and Why did the CRO/Sponsor Require this Data?

- **Full Date of Birth**
- **NHS Hospital Number**
- **Patient's home postcode**

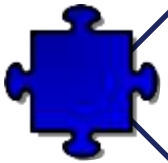
Summary of Root Causes Identified by the CRO

A participant ID was used to pseudo-anonymise participants in the EDC, but the procedure for and the risk assessment itself did not identify that the full extent of personally identifiable data captured



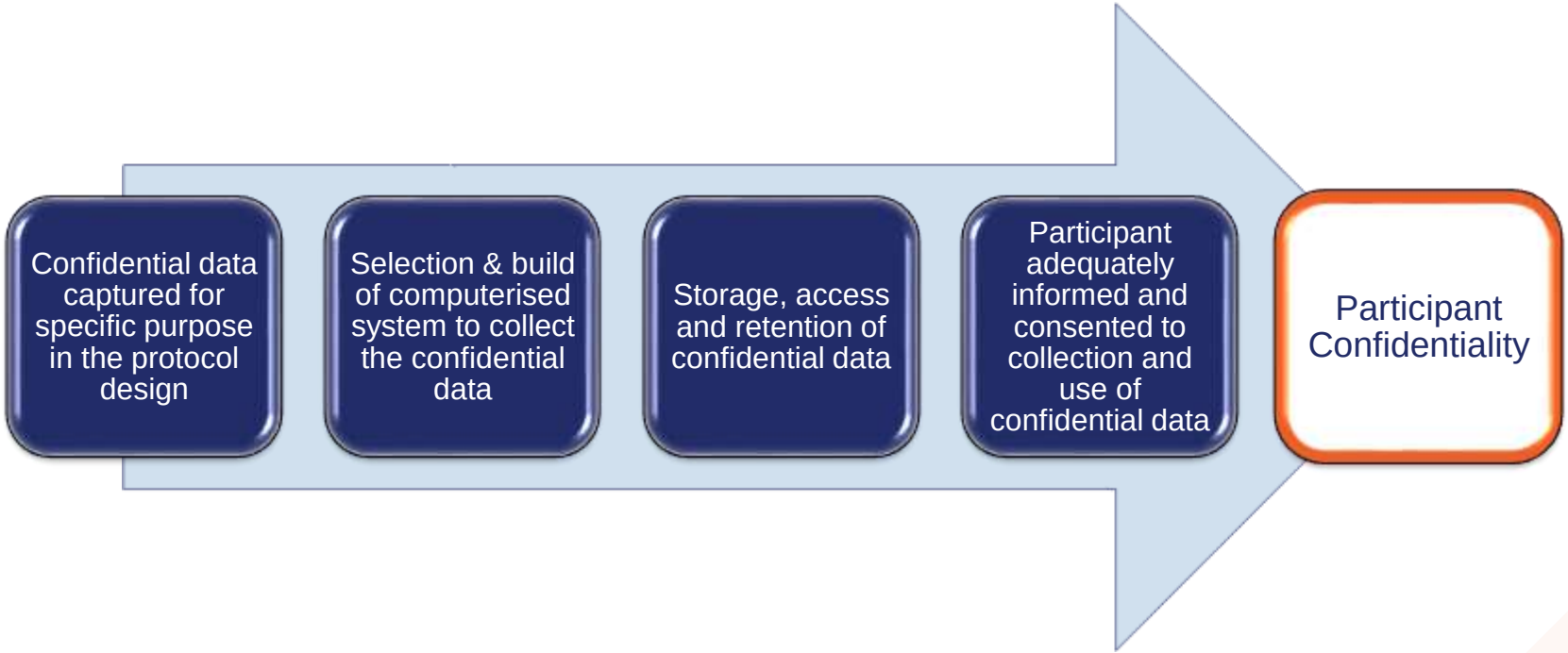
Neither the protocol or CRO process for the preparation, review and approval of the informed consent materials specified what personally identifiable data would be stored/transferred/processed

The procedure for setting up the EDC database did not consider the nature of the personally identifiable data being collected, the details of participant consent, or any required access controls for CRO and Sponsor staff.



There were no procedural controls available on the access and storage of personally identifiable data.

Critical to quality factors



Corrective Actions

Changing the storage location of the identifiable data, liaison with REC on communication to patients regarding the breach and review of other trials for any similar issues

Review and changes to access rights in the EDC

Procedures should be in place to ensure that user access rights are appropriately assigned based on a user's duties and functions, blinding arrangements and the organisation to which users belong. (ICH E6 (R3))

Scripts run by EDC to edit audit trail data.

Ensuring that audit trails, reports and logs are not disabled or modified except in rare circumstances and only if a log of such action and justification is maintained. (ICH E6 (R3))

Preventative Actions

Procedural controls, in accordance with applicable regulatory guidance, for the management of personally identifiable information/personal data, to include:

- risk assessment and risk management
- rationale for capturing
- protocol development & review
- informed consent processes
- access controls in computerised systems
- collection, handling/processing and reporting of data
- final disposition of data and where the data resides

Review of existing organisational training and education in relation to personally identifiable data

In summary, the organisation

Failed to implement an appropriate risk assessment of the protocol design concerning the data to be collected and did not prospectively identify risks to participant confidentiality and implement controls and mitigations. As a result

- Participants were not adequately informed about confidential data to be collected and who would have access and where it would be stored
- Computerised system was designed and built to collect confidential information without any assessment of risk and mitigations required
- Access to confidential information was not appropriately restricted resulting a breach of participants' rights.

Compliance with a risk-based approach to trial conduct, as outlined in ICH E6 (R3), would have prevented these findings and implemented a compliant way to manage this data, if it was necessary to obtain it for the reliability of the trial results.

Processes for Full Data Life Cycle

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ICH E6 (R3) Defining and Documenting the Data Quality Requirements

Ensure that the data are of sufficient quality to generate reliable results for interim & final analysis

Focus quality assurance and quality control activities and data review on critical data

Implement timely and reliable processes for data capture, verification, validation, review & rectification of errors/omissions that have a meaningful impact on the reliability of the trial results.

Data Management steps/activities undertaken, which may vary depending on the purpose of the analysis, to finalise the data sets prior to analysis should be confirmed and documented in accordance with pre-specified procedures.

Activities include reconciliation of entered data/data sets/ databases, correction of data errors & omissions, medical coding, compilation & addressing the impact of non-compliance

Prior to provision of the data for analysis, edit access to the data acquisition tools should be restricted as appropriate to the purpose of the analysis

Applying Risk Proportionality to Data Governance: Case Example on Defining and Documenting Data Finalisation Prior to Analysis

Not Adequately Defining and Documenting the Management of Data Prior to Analysis

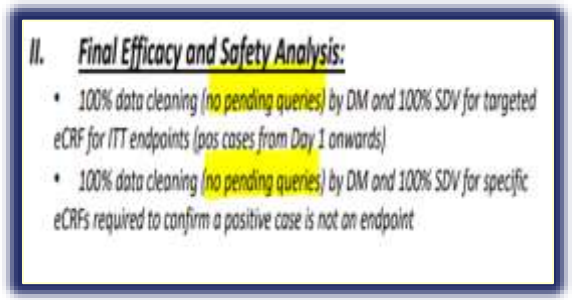
Trial had interim analysis and a final analysis based on number of events reached.

- A powerpoint slide contained details of eCRF screens requiring cleaning. No formalised data cleaning plan or process in place for the interim analysis and to document that such requirements had been met prior to use of the data for analysis.
- The data validation plan did not identify which data and how it would be finalised for the analysis and failed to define the data quality to enable reliable results and decision making.
- An SOP did address data finalization, but this was not applicable to interim analyses.
- For the final analysis there was a Data Finalisation Worksheet completed and signed following data extraction from the database and this documented the data management and cleaning activities completed, but this was not done for the interim analysis.

Not Adequately Defining and Documenting the Management of Data Prior to Analysis (2)

A data cleaning and delivery plan set out expectations for the cleaning of the data for final analyses of all event positive patients

- The Data Finalisation Worksheet for the final analysis stated "***there were queries outstanding that were "unresolvable"***
- A spreadsheet showed queries were not documented as "unresolvable" and that the sponsor had not signed off the queries to be open after undertaking any form of impact review.
- Over 700 outstanding queries included those concerning Adverse Events (risk to primary endpoint), laboratory results (risk to primary endpoint) and participant eligibility (risk that ineligible participants included).

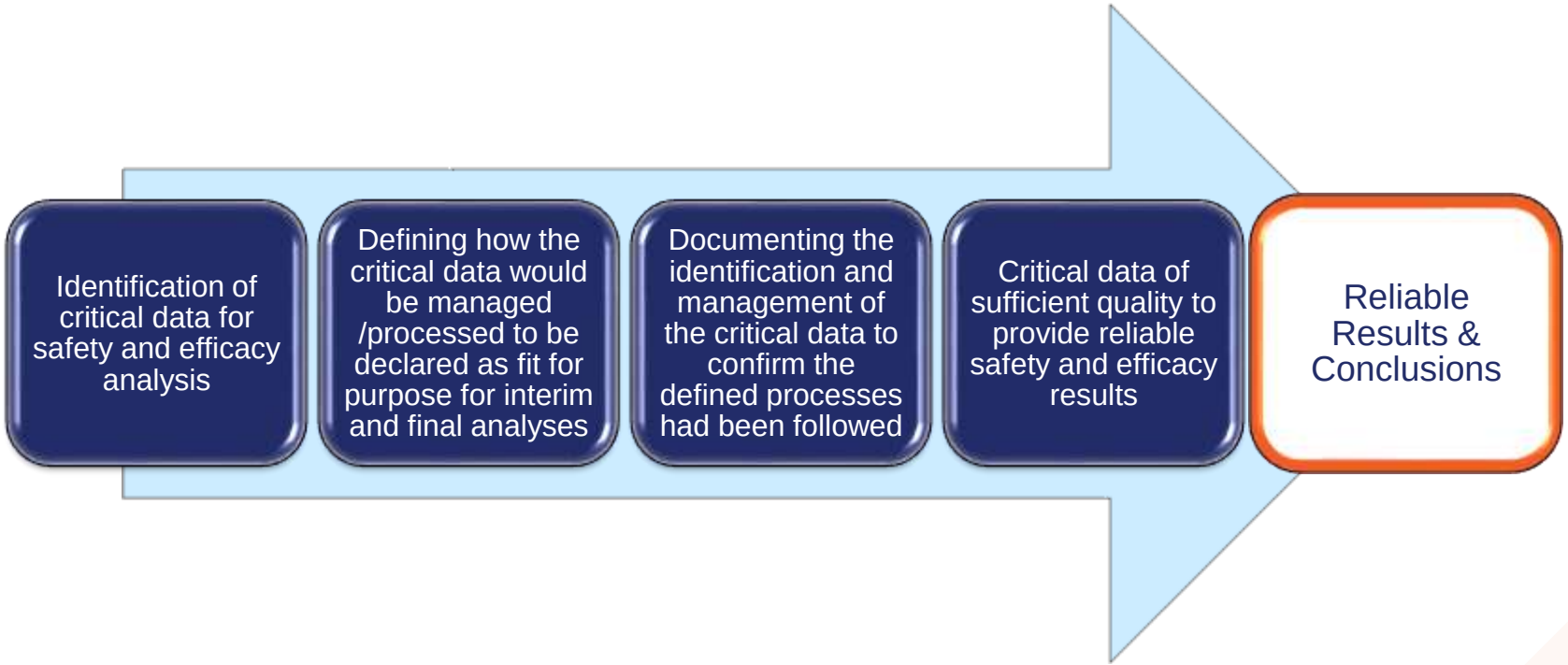


II. **Final Efficacy and Safety Analysis:**

- 100% data cleaning (no pending queries) by DM and 100% SDV for targeted eCRF for ITT endpoints (pos cases from Day 1 onwards)
- 100% data cleaning (no pending queries) by DM and 100% SDV for specific eCRFs required to confirm a positive case is not an endpoint

The sponsor had to undertake an impact assessment to assure that the submitted data to MHRA was reliable for decisions making because of a failure to adequately document both the process itself and that it was followed.

Critical to quality factors



In summary, the organisation

- Had an inconsistent approach to documenting a process for finalising the data for analysis for the interim compared to the final analysis, even though both were used for regulatory decision making.
- Had not followed the documented process for resolution of queries to demonstrate that outstanding issues were unresolvable and that they did not impact on the reliability of the results.

Compliance with a risk-based approach to data governance, as outlined in ICH E6 (R3), would have ensured a focus on critical data, defining its required quality and demonstrating this had been met.

Copyright information

Processes for Full Data Life Cycle

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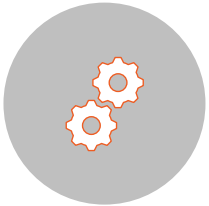
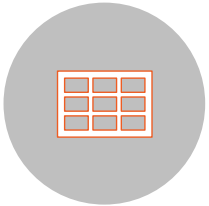


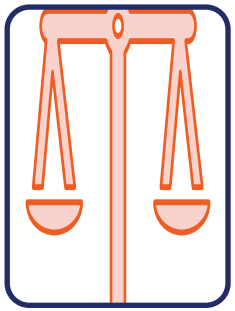
For managing computerized systems to ensure that they are fit for purpose and used appropriately

To safeguard essential elements of the clinical trial, such as randomization, dose escalation and blinding

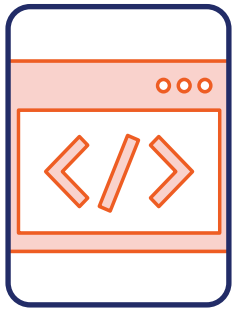


To support key decision making, such as data finalization prior to analysis, unblinding, allocation to analysis data sets, changes in clinical trial design

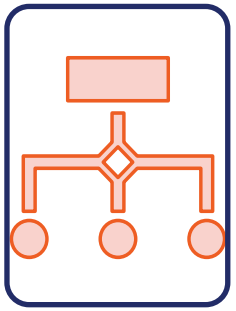
Safeguarding the Trial Blinding



Include the potential for unblinding as part of your risk assessment



Place focus on design/ implementation of computerized systems and processes for maintaining the blind



Define and document roles, responsibilities and procedures for access to unblinded information

Maintain documentation of any planned or unplanned unblinding

Applying Risk Proportionality to Data Governance: Case Example on Maintaining the Integrity of the Blind

Case Example: Background

- Pivotal trial to support approval of an investigational drug was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study
- The ***primary efficacy endpoint*** was a subjective clinician-reported clinical outcome assessment, performed by blinded independent evaluators

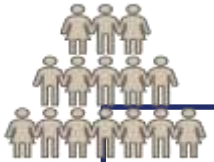
Case Example: Protocol Requirements for Roles & Responsibilities

Independent Evaluators

- Assessed the primary efficacy endpoint
- Were blinded to the treatment assignment, patient data, and adverse events
- Not involved in any aspect of the subject's care and/or disease management

Unblinded Study Team

- Completed early dose adverse event monitoring which could potentially unblind the treatment assignment



Blinded Study Team

- Conducted all other study-related patient care activities (except early dose adverse event monitoring and primary efficacy endpoint assessments)

Case Example: Data Collection and Handling

Independent Blinded Evaluators

Were supposed to have access to and enter data in….

Database 1 which contained primary efficacy endpoint data

Unblinded Study Team

Was supposed to have access to and enter data in…

Database 2 which contained subject information, labs and other test results which if viewed could potentially unblind study personnel to the treatment assignment

Blinded Study Team

Was supposed to have access to and enter data in…

Database 3 which contained all other study information, except for the information in database 1 and 2

Case Example: Data Governance Activities That Are Critical-to-Quality

Critical Data	Clinical Trial Design Elements and Other Important Processes/ Procedures	Critical Data Governance Activities
• Subjective clinician-reported clinical outcome assessment by blinded independent evaluators • Other data that may unblind the blinded study personnel (e.g., early adverse event monitoring)	• Integrity of the blind • Trial roles and responsibilities • Protocol-related training commensurate with roles and responsibilities • RBM strategy tailored to the complexities of the design and the CTQ factors	• User management processes and procedures • Computerized system access controls • Computerized system training of trial personnel commensurate with their role and responsibilities in the trial • Communication of CTQ factors

Case Example: Inspection Observations

User Management Processes

- Were not implemented in a way that was proportionate to the risk to the blinding
- Blinded study personnel were granted inappropriate access to the study database that contained unblinding information
- Unblinded and blinded roles changed throughout the trial at many sites with unblinded team members switching roles midway through the trial to serve as a blinded team member and/or be independent evaluators

Communication and Training

- Was insufficient because study personnel did not understand what data and study-related activities were critical-to-quality and the importance of their role in ensuring the maintenance of the blind

Monitoring

- Was not tailored to the complexities of the trial design and maintaining the blind

Case Example: Data Reliability Assessment and Its Implications

Blinding was not adequately maintained as specified in the protocol throughout the course of the trial affecting the reliability of the study data

The introduction of study bias could not be ruled out because study subjects had their study assessments performed by blinded study team members who were unblinded

Sensitivity analysis was conducted with respect to the subject study data that was impacted by the inappropriate access

Closing Thoughts

- Identify critical data and processes that if inaccurate, not performed, or performed incorrectly, would threaten the protection of trial participants or the integrity and reliability of the study results
- Ensure input from all trial personnel in the study planning, including data scientists and key service providers
- Focus your resources on the data and data governance activities that are critical-to-quality
- Proactive communication to all study personnel of what data and processes are critical-to-quality will support their understanding of the priorities and resource allocation by the sponsor and investigator sites
- Individuals involved in study conduct should receive training commensurate with their role
- Monitoring should reflect the critical-to-quality factors

Questions?