AS03- Blinded & Coordinated: Aligning People and Processes to Prevent Unblinding

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Agenda

➤ Clinical Trial Design Essentials: Randomization, Blinding and Unblinding

➤ Risks

➤ Coping Strategies, including Possible Scenario of Accidental Unblinding

➤ Team Responsibilities

➤ System Considerations

➤ Communication & Documentation Best Practices

➤ Conclusions

Clinical Trial Design Essentials: Randomization, Blinding, and Unblinding

- **Randomized Participant Allocation**

Randomization ensures unbiased distribution of participant in clinical trials.
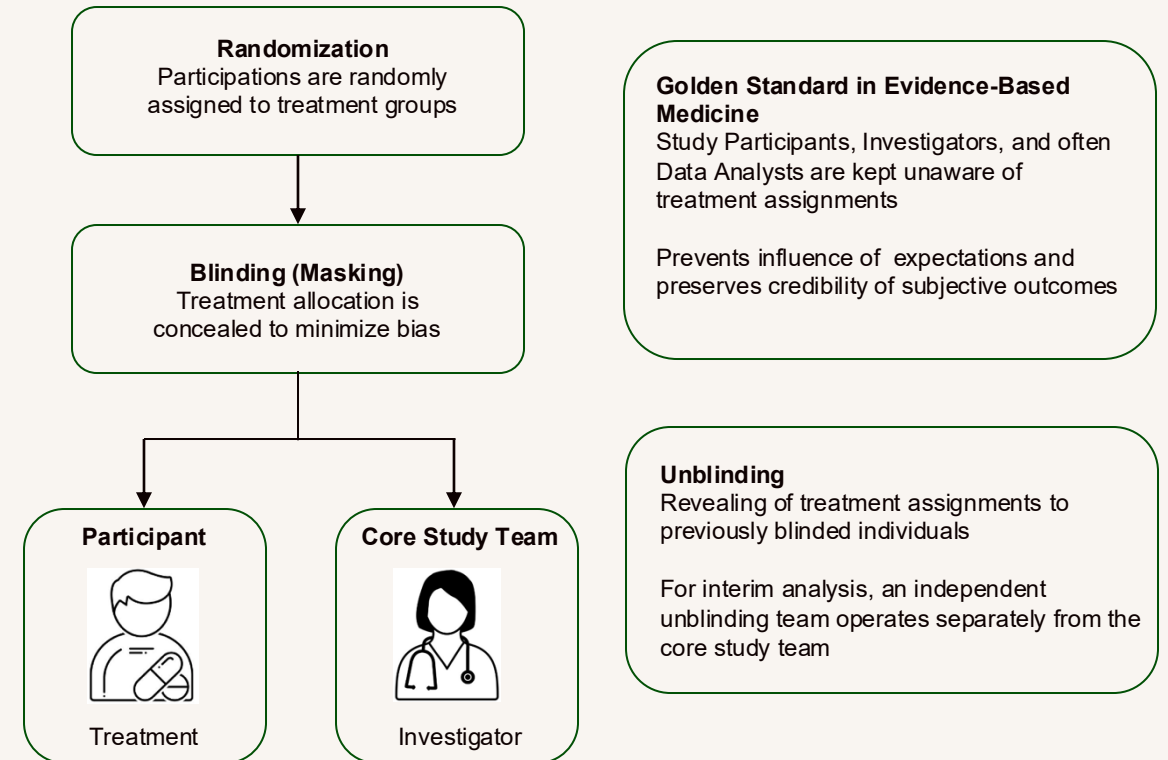
- **Principle of Blinding**

Blinding keeps participants and investigators unaware of treatments to reduce bias in clinical trials.

- **Double-Blind Trials**

Double-blind trials prevent expectation influences and protect subjective outcome credibility.

- **Controlled Unblinding**

Unblinding reveals treatment assignments under strict conditions for safety or interim assessment purposes.

Randomization
Participations are randomly assigned to treatment groups

Blinding (Masking)
Treatment allocation is concealed to minimize bias

Participant

Treatment

Core Study Team

Investigator

Golden Standard in Evidence-Based Medicine
Study Participants, Investigators, and often Data Analysts are kept unaware of treatment assignments

Prevents influence of expectations and preserves credibility of subjective outcomes

Unblinding
Revealing of treatment assignments to previously blinded individuals

For interim analysis, an independent unblinding team operates separately from the core study team

Risks of Accidental Unblinding

- **Direct Risks from Randomization data**

Randomization data managed by external vendors can directly reveal treatment assignments if not properly secured.

- **Indirect Risks from PK, PD, and Lab Data**

Pharmacokinetic (PK), pharmacodynamic (PD), and safety lab data may indirectly disclose treatment allocation if not treated with care. Risks increase if:

  - Data Transfer Specification (DTS) does not flag unblinding parameters.
  - Contents of blinded transfer are unclear.
  - Comments fields inadvertently reveal treatment.

- **Operational Errors and Oversights**

Human errors like mislabeling and/or mis-filing files and poor documentation increase unblinding risks in data transfers.
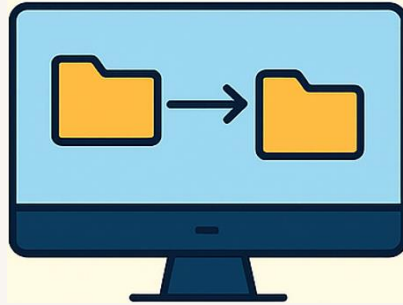
- **Importance of Robust Controls**

Implementing strict controls and clear documentation is vital to prevent accidental unblinding in trials.

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Coping Strategies

Implementing SOPs

Standard Operating Procedures help mitigate unblinding risks by establishing clear protocols for data handling.

Assessing Data Transfers

Proactive assessment of data transfer specifications ensures identification of potentially unblinding data.

Collaboration & Governance

Internal collaboration between blinded and unblinded teams supported by governance improves corrective actions.

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Accidental Unblinding – Possible Scenario

- **Scenario**: An unexpected case occurs involving the external transfer of blinded PK data. During reconciliation, it is observed that a subset of subjects is missing from the transfer file, even though the clinical database confirms PK samples were collected.

- **Potential Corrective Actions:**

  - Immediate removal of the file from the server and deletion of all backups.

  - Reassignment of any team members who accessed the unblinded data.

  - Creation of a formal Corrective and Preventive Action (CAPA) document to address root causes, implement safeguards, and capture lessons learned to prevent recurrence.

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Blinded and Unblinded Team Responsibilities
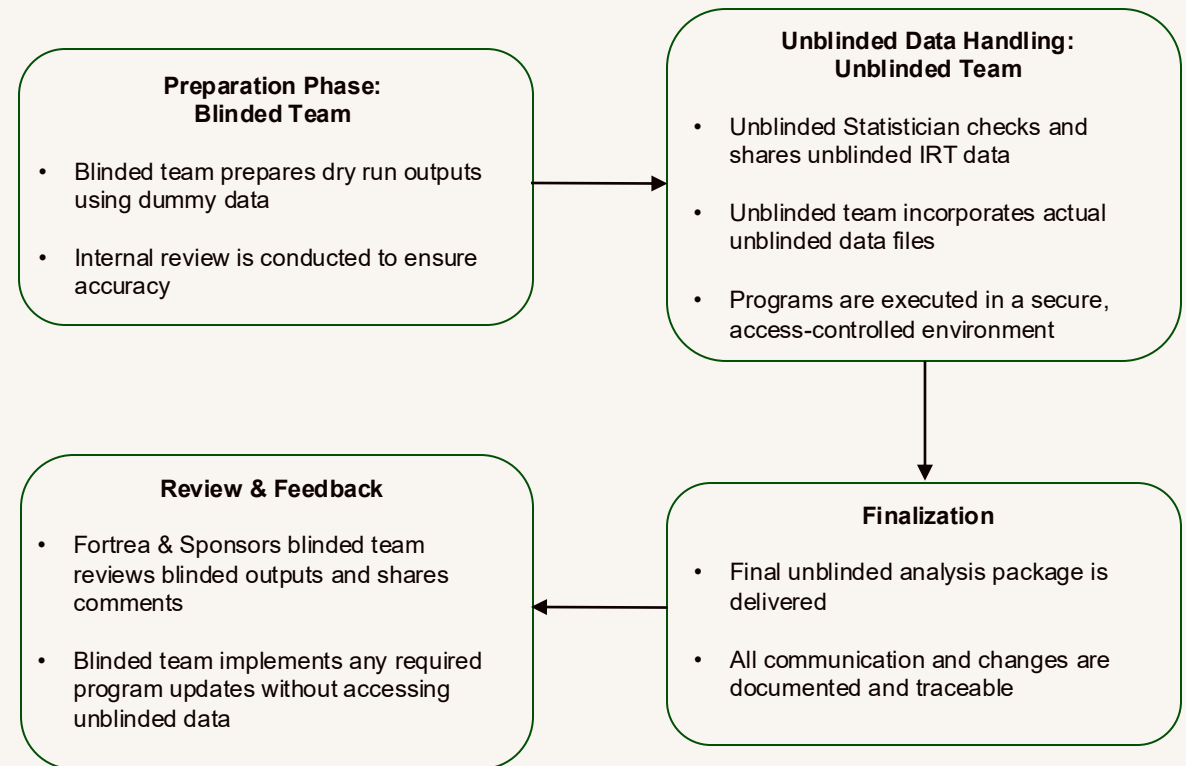
- **Blinded Team Responsibilities**

The blinded team prepares analysis programs using dummy data and conducts dry runs during interim study phases.

- **Unblinded Team Execution**

Unblinded team executes programs securely with actual unblinded data after database lock to ensure accuracy.

- **Communication and Data Security**

Careful communication prevents data disclosure while maintaining program ownership and trial integrity.

Preparation Phase: Blinded Team

- Blinded team prepares dry run outputs using dummy data
- Internal review is conducted to ensure accuracy

Unblinded Data Handling: Unblinded Team

- Unblinded Statistician checks and shares unblinded IRT data
- Unblinded team incorporates actual unblinded data files
- Programs are executed in a secure, access-controlled environment

Finalization

- Final unblinded analysis package is delivered
- All communication and changes are documented and traceable

Review & Feedback

- Fortrea & Sponsors blinded team reviews blinded outputs and shares comments
- Blinded team implements any required program updates without accessing unblinded data

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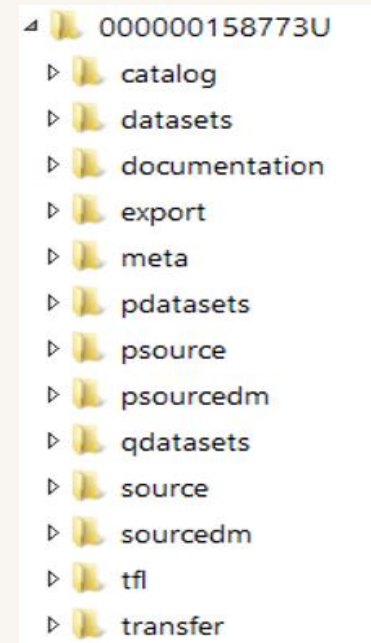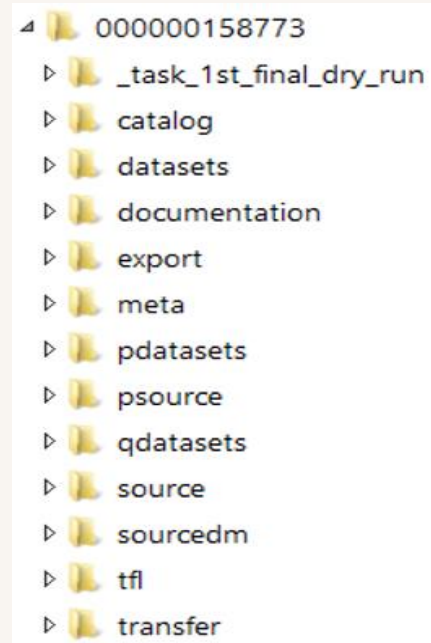# System Considerations

- **Identical Folder Structure**

Using the same folder structures for blinded and unblinded areas simplifies program execution but introduces access risks.

- **Access Control Models**

Two access models are used: default open with restricted areas and role-based access for stronger protection.

- **Data Transfer Security**

Secure, restricted connections ensure unblinded data is safely transferred to sponsors with controlled folder access.

Communication & Documentation Best Practices

- **Clear Role Separation**

Define distinct roles to prevent accidental unblinding and maintain clarity in team responsibilities.

- **Controlled Handover Processes**

Use structured handovers with user guides, audit trails, and version control to ensure accurate communication.

- **Training and Standard Operating Procedures (SOPs)**

Provide training and standard operating procedures to guide interactions and reinforce blinding principles.

- **Transparent Issue Reporting**

Report issues from unblinded teams back to blinded teams without sharing sensitive data to ensure compliance.

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Conclusions

- **Collaboration Benefits**

Integrated blinded and unblinded teams improve operational efficiency and reduce delays in data processing and communication.

- **Standardized Practices**

Shared coding standards and infrastructure ensure consistent programming and minimize risks of misalignment and errors.

- **Transparency and Documentation**

Centralized documentation and audit trails promote transparency and accelerate interim analyses within the organization.

- **Training and Safeguards**

Comprehensive training ensures awareness of workflows and safeguards to prevent accidental unblinding and maintain compliance.

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Thank You
Any Question?

Contact Information

- Your comments and questions are valued and encouraged. Contact the authors at:

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