Safeguarding Blinding in Data Governance

ICH E6 R3 – Good Clinical Practice

Who, What, When, Why and How?

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Purpose Statement

Changes in the clinical trial ecosystem mean that **safeguarding of the blind** becomes more challenging due to **innovation in trial design, technology and operational approaches.** Clarity on data collection and flow in the trial helps the sponsor ensure that any action at any point is appropriately conducted to protect blinding of multiple data sources.

This solution helps internal and external stakeholders understand **who, what, when, why, and how to safeguard the blind** throughout the trial lifecycle.

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Who - Which Stakeholders are Involved in Safeguarding the Trial Blind?

Click on the boxes to know more about the stakeholder involvement in the trial blind process.
To go back to this slide, click the blue arrow at the right bottom angle of the slides.

Internal Stakeholders*

- Statistics – Biostatistician and stat programmer
- Data Management
- Trial Management
- Investigational Medical Product (IMP)
- Monitoring – Site, Central, Medical
- Safety Management
- Computer system design and validation

External Stakeholders

- Healthcare Professionals and Site Staff
- Outcome Assessors (e.g., Radiology, Pathology)
- Outcome Assessors (Trial Personnel Gathering Outcome Data)
- Independent Review Committees
- Participants
- Vendors and Central Laboratory
- Pharmacy Staff

*Internal stakeholders can be from the clinical trial sponsor or the CRO, depending on the model used for the trial. The sponsor is ultimately accountable for the reliability of the clinical trial results and protection of participants' rights and safety.

What Records and Processes Might Impact the Trial Blind?

Records
• Randomization file • Participant trial data that might lead to unblinding of individual's treatment assignment • Interactive Response Technology (IRT) reports may be a common source of unblinding due to either inappropriate access or email distribution • Investigational Medicinal Product (IMP) manufacturing records

Processes
• "The potential for unblinding should be part of the risk assessment of a blinded trial". (ICH E6 R3 4.1.3) • Controls on data transfers including Data Transfer Agreements, if applicable • Development and finalization of Statistical Analysis Plan • Computer system design and implementation • Validation and User Acceptance Test (UAT) • User access/account control • Control of treatment assignments/Randomization schedules • Segregation of blinded and unblinded roles on trial team • Delegation of responsibilities with respect to data handling and provision of data access • Any planned or unplanned unblinding, including accidental or emergency unblinding, should be documented and assessed for impact to trial results. • Controlled distribution of safety reports • Secure data storage • Database review prior to unblinding • Finalization of statistical analysis prior to unblinding

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Sponsor – Statistics (Statisticians and Statistical Programmers)

Internal Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 Section 6.1.4)

Information withheld: Treatment allocation, Participant trial data that could lead to potential unblinding

What

- "Roles, responsibilities and procedures for access to unblinded information should be defined and documented by all relevant parties according in the protocol" (ICH E6 R3 4.1.2)
- Where generation of randomization code is performed within statistics , consideration should be given to how this process is performed to prevent unblinding
- "Full details of the planned statistical analysis plan should be specified and documented before knowledge of the study results" (ICH E8 R1 5.6)
- Access control: "In studies with planned interim analyses, special attention should be given to which individuals have access to the data and results. In studies without planned interim analyses, special attention should be paid to any ongoing monitoring of unblinded data to avoid inappropriate access. "(ICH E8 R1 6.1.4)
- "In blinded (single or double blinded) trials, sponsor staff or designated third parties who are involved in operation of the trial and directly or indirectly interact with site investigator staff should not have access to unblinding information." (ICH E6 R3 section 4.1.2)
- "In double blinded studies, the statistical analysis should be finalised before treatment assignments are revealed" ICH E8 R1 5.6)

When

- Trial start up to unblinding for interim and final data analysis

Sponsor – Data Management

Internal Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)

Information withheld: Treatment allocation, Participant trial data that could lead to potential unblinding

What

- Case report form design
- Laboratory Reports design including PK reports (if applicable to trial design)
- Sponsor should document the data management steps to be undertaken prior to data analysis.
- Customized report generation for blinded/unblinded roles
- Process for information flow should be specified for interim and final analyses including Data transfers and Data reporting.
- In studies with planned interim analyses, special attention should be given to which individuals have access to the data and results.

When

- Trial start up to results reporting

Sponsor – Trial Management

Internal Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)

Information withheld: Treatment allocation, Participant Identities

What

- Separate blinded and unblinded roles
- Controlled emergency unblinding process
- Providing ongoing input for trial design and conduct, which may lead to amendments to the clinical trial protocol
- Defined process for information and data flows between Sponsor and Site, Vendors including:
  - Process for randomization
  - Protocol Deviations, Issue Reporting and assessment
  - Communication of safety information
  - Provision for emergency unblinding
  - Unblinded and Blinded monitoring reports
- Controlled distribution of Topline results dissemination from interim analysis

When

- Trial start up to results reporting consistent with role in the trial

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Sponsor – Investigational Medical Product (IMP)

Internal Stakeholders

Why

- Inappropriate access to data during the conduct of the trial may compromise trial integrity (ICH E8 Section 6.1.4)

Information withheld: Treatment allocation, Participant Identities

What

- Manufacturing, handling and labelling of investigational products should be undertaken in a manner that aligns with treatment assignment and maintains blinding.
- Enhanced processes and other mitigations to be put in place where identical placebo match is not possible
- Separation of blinded and unblinded roles
- Identification by code on invoicing and stock management for blinded trials.
- User account management for IRT/IVRS systems according to trial roles
- Design of reports and notifications from IVRS to preserve the blind
- Restricted distribution lists for IMP information based on role

When

- Trial start up to results reporting consistent with role in the trial

Sponsor - Oversight, Site, Central, and Medical Monitoring

Internal Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)

Information withheld: Treatment allocation, Participant Identities

What

- User account management and training for electronic systems
- Separate blinded and unblinded roles

When

- Trial start up to results reporting consistent with role in the trial

Sponsor – Safety Management

Internal Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)

Information withheld: Treatment allocation, Participant Identities

What

- Separation of blinded and unblinded process for Individual Case Safety Review and review of aggregate line listings
- Controlled distribution list for unblinded safety reports
- Separate blinded and unblinded roles

When

- Trial start up to results reporting consistent with role in the trial

Sponsor – Computer System Design and Validation

Internal Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)

Information withheld: Role based access to unblinded information

What

- Risk assessment based on system use and data contained within the system
- System design and validation
- System security and access control
- Data transfer/Import/Interfaces
- System training
- System error management
- Software/System vendor oversight
- Vendor contracts

When

- Trial start up to results reporting consistent with role in the trial

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External – Healthcare Professionals (HCP) and Site Staff

External Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)

Information withheld: Treatment allocation, Participant Identities

What

- Drug dispensing information
- Treatment Administration
- IMP labelling
- Drug shipment and returns
- Local lab test, which may unblind if the active IMP affects a particular parameter
- prevalence of a certain adverse event may also indicate either the test drug/comparator or placebo

When

- Trial start up to results reporting consistent with role in the trial

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External – Outcome Assessors (Trial Personnel Who Collect Outcome Data)

External Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)
- Bias due to influence of trial team on outcome assessment

Information withheld: Treatment allocation, Participant Identities

What

- Risk assessment of data flow for outcomes data
- Appropriate assessment of vendors prior to trial start up to ensure capabilities to protect the blind
- Access control for vendor systems
- Segregation of roles and communication pathways

When

- Trial start up to results reporting

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External – Independent Data Monitoring Committees

External Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)

Information withheld: Treatment allocation, Participant Identities

What

- Controlled meeting attendance
- Controlled Communication pathways for sharing trial data with committees
  - Defined distribution lists
  - Restricted access to unblinded team members
- Controlled Data transfers
- Defined distribution list

When

- Trial start up to results reporting consistent with role in the trial

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External – Participants

External Stakeholders

Why

- "Participant knowledge of their group allocation can bias expectations, adherence to trial protocol, treatment seeking behaviour outside the trial and assessment of the effectiveness of an intervention, impact on retention of participants who are on placebo or reference treatment"(Monaghan, 2021)

Information withheld: Treatment allocation, Participant Identities

Monaghan TF, Agudelo CW, Rahman SN, Wein AJ, Lazar JM, Everaert K, Dmochowski RR. Blinding in Clinical Trials: Seeing the Big Picture. Medicina (Kaunas). 2021 Jun 24;57(7):647. doi: 10.3390/medicina57070647. PMID: 34202486; PMCID: PMC8308085."

What

- Drug dispensing information
- Treatment Administration
- Investigational Medicinal Product (IMP) labelling
- Drug shipment and returns

When

- Trial start up to results reporting

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External – Vendors and Central Laboratory

External Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)

Information withheld: Treatment allocation, Participant Identities

What

- Computer system design and validation of systems used for trial
- User account management and training for electronic systems
- Contractual agreements
- Data transfer
- Controlled distribution lists for reports
- Defined format reports
- Controlled distribution lists for investigations/issue reporting

When

- Trial start up to results reporting consistent with role in the trial

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External – Pharmacy Staff

External Stakeholders

Why

- "Inappropriate access to data during the conduct of the study may compromise study integrity" (ICH E8 R1 6.1.4)

Information withheld: Treatment allocation, Participant Identities

What

- Handling of code break envelopes or other processes for emergency unblinding
- Controlled access for randomization documents and other methods used for randomization
- Aseptic preparation of IMP
- Communication with the Research Team
- Communication with the Sponsor
- Invoicing and stock management for blinded trials
- Destruction of IMP
- Training

When

- Trial start up to results reporting
- Trial results up to unblinding for analysis

How to Safeguard the Trial Blind?

Key processes to safeguard the trial blind include:

- Prospectively identify which data, computerized systems, and data governance processes are important to maintain the blind
- Identify protection of the blind as being critical to quality and prospectively identify and mitigate opportunities for error that could result in inadvertently providing inappropriate access to blinded information
- Focus on design/implementation of computerized systems and processes for maintaining the blind
  - System development personnel are familiar with the use to which system will be put
  - Sponsor validation and confirmation of systems as fit for purpose
  - System and trial Training
  - Access controls and user account management
  - System issue management and error resolution
  - Vendor oversight and management
- Define and document roles, responsibilities and procedures for access to unblinded information. Protocol should describe the blinding controls in a trial.
  - Blinded and Unblinded team roles
  - Maintain documentation of any planned or unplanned unblinding
- IMP Manufacture, labelling and shipment processes designed to maintain the blind

Special Considerations for Non-Traditional Trial Types

- "Pre-specification of the analysis approach is particularly important for studies that make use of existing data sources rather than primary data collection (Section 5.7), not only for the statistical analysis planned for the trial but also for any feasibility analysis to assess the applicability of the existing data".(ICH E8 R1 5.6)
- ".. the use of internal controls generally mitigates the potential for bias better than external controls, particularly in conjunction with randomisation, the suitability of the use and choice of external control should be carefully considered and justified." (ICH E8 R1 5.3)
- "There may also be differences in the follow-up patterns between the groups due to participants in one group discontinuing the trial at different rates, due to, for example, adverse events or perceived lack of efficacy" (ICH E8 R1 5.5). Consider how this might impact the blind for the trial.

Special Considerations - Decentralized, Point of Care (POC) and Pragmatic Trials

- Data quality principles are the same for clinical trials using digital technologies for data capture and those using data collection approaches in the clinic.
- **Determine which activities must occur at the investigative site, a local or mobile HCP, and which are amenable to remote technology solutions and evaluate the data flows accordingly**
  - Include maintenance of the blind in risk assessment for the entire dataflow as for trials with a standard design
  - Consider if additional trial safeguards, processes, training, and/or procedures are required to maintain the blind for novel technologies and processes
  - Designate where and how local source documents and electronic information will be stored to protect the blind
  - Consider regional differences in remote technology availability
- **Manage relationships with non-trial personnel (e.g., local HCPs), facilities (e.g., local clinical laboratories and imaging services).**
  - Consider risks to trial blind during the communication and dataflows for these activities.
  - Determine any additional training needed for control of blind where telehealth visits and Digital Health Technologies (DHTs) are used
- **Sponsors/CROs should ensure that digital health technologies (DHTs) are available and suitable for use by all relevant participant populations.**
  - Given the increased use of computerized systems and the increased complexity of the data flow, sponsor oversight is correspondingly more important to ensure adequate and close oversight of trials with decentralized elements (including maintenance of the blind)
- **Monitoring activities should assess maintenance of the blind from the different data sources**

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