(Un)Blinding points to consider

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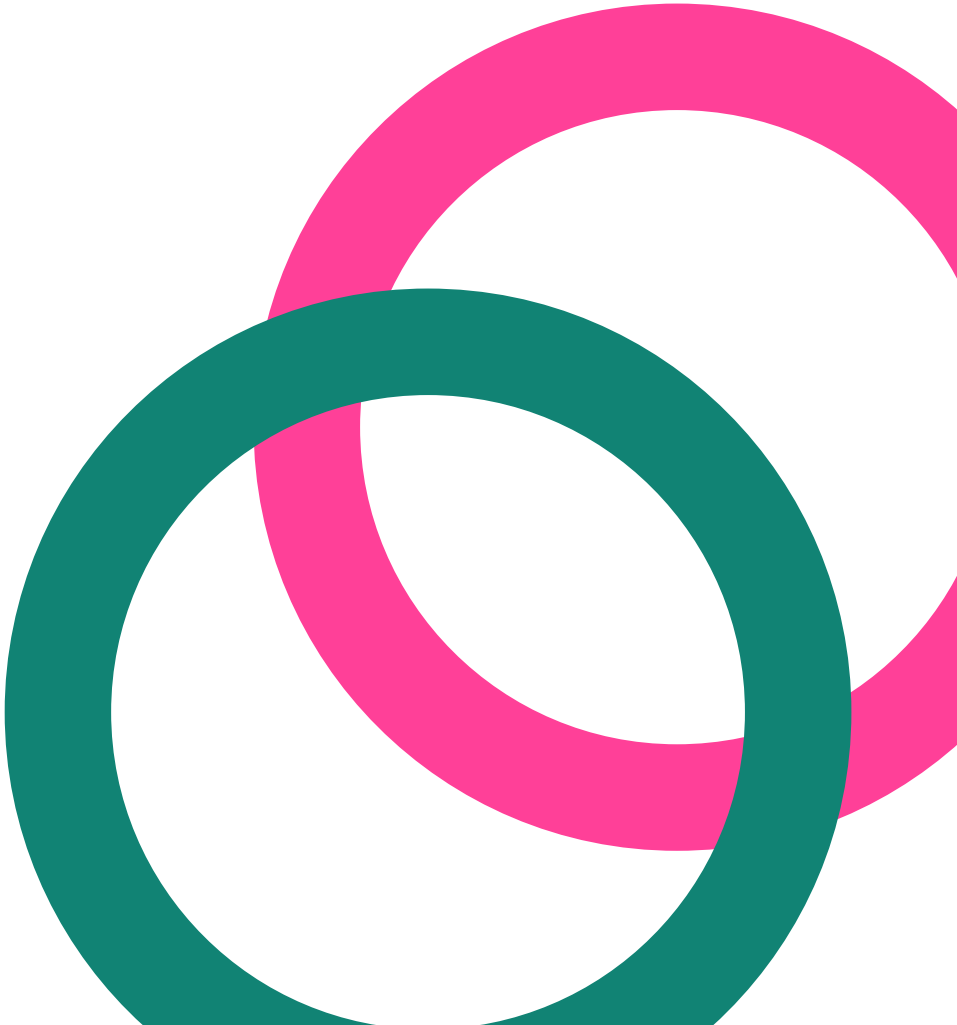

TOPICS

- Why Blinding & What to blind
- Consequences for SDTM
- Dummying Data
- Pitfalls and mitigation
- Q&A / Discussion

Why Blinding & What to blind

Why Blinding?

ICH E9 STATISTICAL PRINCIPLES FOR CLINICAL TRIALS) dated 5 February 1998. GUIDELINE FOR GOOD CLINICAL PRACTICE (ich.org)

- Chapter 2.3 Design Techniques to avoid Bias,
  The most important design techniques for avoiding bias in clinical trials are blinding and randomisation, and these should be normal features of most controlled clinical trials intended to be included in a marketing application.

- Chapter 2.3.1 Blinding
  Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and ***interpretation of a clinical trial*** *arising from the influence which the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments,* ***the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis,*** *and so on. The essential aim is* ***to prevent identification of the treatments until all such opportunities for bias have passed.***

Why Blinding?

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2), current Step 4 version dated 9 November 2016

GUIDELINE FOR GOOD CLINICAL PRACTICE (ich.org)

- Glossary 1.10: Blinding/Masking
- Chapter 4.7: Randomization Procedures and Unblinding
- Chapter 5.5: Trial Management, Data Handling, and Record Keeping
- Chapter 5.13: Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)
- Chapter 6.4: Trial design.

Why Blinding?

ICH E6(R3): Draft version, Endorsed on 19 May 2023

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

– Chapter 3.15.2 Manufacturing, Packaging, Labelling and Coding Investigational Product(s):

d) *In blinded trials, the sponsor should implement:*

(i) *a process to blind the sponsor staff, trial participant and/or investigator as appropriate to the investigational product identity and assignment to prevent and detect inappropriate unblinding;*

(ii) *a procedure and mechanism that permits the investigator to rapidly identify the product(s) in case of a medical emergency where unblinding is considered necessary, while protecting the identity of the treatment assignment of the other trial participants;*

(iii) *a mechanism that protects the blinding of the trial where a participant's treatment assignment is unblinded for the purpose of safety reporting to regulatory authorities and/or IRB/IEC, where appropriate*

What to blind?

Unblinding potential

- The knowledge of
  - treatment assignment
  - Dosage of active ingredient if different between investigational product and control
  - Lab values if revealing the treatment
  - PK values since revealing the treatment

No unblinding potential

- The knowledge of the treatment names ➡ they are in protocol.
- The knowledge of a lab or PK parameters name ➡ that is in protocol.

Consequences for SDTM

Consequences for SDTM

Trial design domains

- no impact since mirroring the protocol

DM: ARMC, ARM, ACTARMCD, ACTARM

- Dummy/masked values while blinded
- Real values when unblinded

EC: ECTRT

- Masked value or the string ‘MASKED’ in blinded studies
- Real values in open-label studies.
- Does not change after unblinding ➡ see SDTM IG 3.2-chapter EC bullet point 2.
  In an open-label study, ECTRT should store the treatment name. In a masked study, if treatment is collected and known as Tablet A to the subject or administrator, then ECTRT = ‘TABLET A’. If in a masked study the treatment is not known by a synonym and the data are to be exchanged between sponsors, partners and/or regulatory agency(s), then assign ECTRT the value of ‘MASKED’

Consequences for SDTM

EX: EXTRT, EXDOSE, EXDOSTOT

- Dummy/masked values while blinded
- Real values when unblinded

PC: PCORRES /PCSTRESN/PCSTRESC

- Dummy/masked values while blinded
- Real values when unblinded

Dummying Data

Dummying Data

How to dummy data:

- Assign treatments to subjects at random,
  - using treatment name as provided by IVRS vendor
- Assign PK values at random but consistent to the dummy treatment
  - Preferable mirroring the live data e.g.
    - values within and outside possible lower and upper limit,
    - increasing value if dose escalation

Dummying Data

Why dummying data?

- Allows finalization of programs and domains prior to unblinding
- Allows PK specialist to prepare the analysis upfront

➡ Allows usage of the same programs for unblinded IA analysis or DSMBs, DMCs etc.

➡ Less time between DB lock and Topline results.

Pitfalls and Mitigation

Pitfalls and mitigation

1) Unblinded team stores unblinding information (data, results) in unrestricted area, blinded team has access to unblinded information

- No write access to public area for unblinded team
- No access at all to unblinded area for blinded team

2) (IVRS, PK or Lab) Vendor provides unblinded file by mistake

- Set up process that prevents unblinded file received by study team

  a) file always received by independent individual (at ICON – System developer/ system designer)

  b) independent individual blinds the data before releasing to study team

Pitfalls and Mitigation

3) Study design requires lab parameter ‘A’ to be collected only when lab parameter ‘B’ is elevated with lab parameter ‘B’ being impacted by study treatment

➡ Lab parameter ‘A’ only collected for subjects taking study treatment and thus already the presence of the parameter is unblinding

- Blind both Lab Parameters
- Collect Lab parameter ‘A’ for all subjects independently of Lab parameter ‘B’ result

Pitfalls and Mitigation

4) Unblinded programming team detects programming issue for a particular subject not occurring with dummy data

➡ telling the subjects name or even the circumstance could unblind since then the blinded team would know for sure that this subject does not have the dummy treatment

- High level communication to ensure not to reveal subject

Pitfalls and Mitigation

5) Unblinded programming team detects programming issue for a particular subject not occurring with dummy data

- ➡ telling the subjects name or even the circumstance could unblind since then the blinded team would know for sure that this subject does not have the dummy treatment
- High level communication to ensure not to reveal subject

6) Laboratory value with unblinding potential due to issue in blinding script

- Code review of script
- Re-review of blinded data before releasing to unblinded team
- Setting up an unblinded programming team that receives and checks the data first.

Pitfalls and Mitigation

7) Blinding of raw drug accountability data failed due to an erroneous update of blinding script.

- ➡ Unblinded data went to SDTM and then to wider team
- ➡ Issue potential not visible before releasing to blinded team due to special process of releasing data

Programmatic check of data if indeed blinded by

a) blinded programmer ➡ This would still mean parts of the blinded team being unblinded but not wider team

b) unblinded programmer ➡ This would ensure none of the blinded team gets unblinded

Q&A / Discussion

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