MAINTAINING THE BLINDING DURING THE TRIAL: MONITORING, DATA REVIEW, INTERIM ANALYSIS, DSMB, SAES

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1. Why blinding is important?
2. How to maintain the blinding?

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1. Why blinding is important?

i. The blinding minimize the bias due to human behaviour

ii. Bias due to human behaviour cannot be measured

1. Why blinding is important?

i. The blinding minimize the bias due to human behaviour

Human behavior is influenced by what we know, what we believe, and our temptation to find out what is going on.

Human behavior lead to biased results in clinical trial. The bias due to human behavior is one of the major threats to scientific validity.

- Come from several sources
- It is silent, invisible
- Validity of the results can be questioned from authorities

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1. Why blinding is important?

ii. Bias due to human behaviour cannot be measured

Human behaviour bias cannot be measured.

One of the established and fundamental principles for avoiding the problem of human behaviour bias is to keep the study participants and the investigators blinded to the identity of the assigned intervention.

1. Why blinding is important?

ii. Bias due to human behaviour cannot be measured

Although many seem to agree that to adopt some form of blinding whenever relevant, blinding is usually simply reported as being accomplished (with a sentence or two routinely added in the protocol and publications, especially in the title and keywords). The success of blinding procedures and/or status is rarely measured or reported.

Many authoritative statements and/or recommendations on blinding have been put forth, especially from FDA which often recommended a questionnaire at study completion to investigate the effectiveness of blinding

Because the effectiveness of blinding is typically NOT measured, **monitoring of the blinding needs to be proved** along all the study duration.

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1. Why blinding is important?
2. **How to maintain the blinding?**

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2. How to maintain the blinding?

i. Avoid any possible link between Patient ID and Rando list before DBL/Unblind

ii. Avoid potentially unblinding data readiness before DBL/Unblind

2. How to maintain the blinding?

i. Avoid any possible link between Patient ID and Rando list before DBL/Unblind

ISSUE / CHALLENGE

CRF – Randomization form

Patient ID	Randomization ID
001001	0001
001002	0002
001003	0003
001004	0004
001005	0005

CRF – Drug accountability form

Patient ID	Kit ID
001001	001A
001002	001B
001003	001C
001004	001D
001005	001E

Randomization list

Randomization ID	Treatment
0001	ACT_200mg
0002	ACT_200mg
0003	**Placebo**
0004	ACT_200mg
0005	ACT_200mg
0006	**Placebo**
0007	ACT_200mg
0008	ACT_200mg
0009	**Placebo**
0010	ACT_200mg
0011	ACT_200mg

Kit list

Kit ID	Treatment
001A	ACT_200mg
001B	ACT_200mg
001C	**Placebo**
001D	ACT_200mg
001E	ACT_200mg
001F	**Placebo**
001G	ACT_200mg
001H	ACT_200mg
001I	**Placebo**
001L	ACT_200mg
001M	ACT_200mg

NB: For not randomized trail the issue / challenge is reflected only in the kit list

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2. How to maintain the blinding?

i. Avoid any possible link between Patient ID and Rando list before DBL/Unblind

SOLUTIONS and ADEQUATE PROCEDURES 1/2

Throughout the trial blinded period, only pre-identified designated personnel, not directly involved in the study is allowed to have access to the treatment information

Reporting related activities like programming should be planned and performed before DBL/unblinding. These can be performed in blinded fashion (using dummy rando and kit lists).

Standard operating procedures (SOP) must be in place for unplanned unblinding during the trial conduct, e.g. in case of emergency unblinding due to a subject's drug-related medical emergency, drug-related AE or SAE etc.

2. How to maintain the blinding?

i. Avoid any possible link between Patient ID and Rando list before DBL/Unblind

SOLUTIONS and ADEQUATE PROCEDURES 2/2

Adequate standard procedure (typically charters) are required also for planned unblinding. Planned unblinding is needed for data safety monitoring board (DSMB) and for interim analysis (IA).

- DSMB ➔ A team of independent expert who periodically review safety data. DSMB need rando and kit list information before DBL/unblinding.
  - List authors should send live rando and kit list only to the DSMB, in a protected manner

All these data transfers, including involved persons, folders, etc. should be well planned and described in SOP and DSMB charter

- IA ➔ At IA an independent biometrics team (statistician and programmer) should perform the analysis. Independent biometrics team should not be involved in any start-up tasks (SAP, set-up of programs, strategic decisions, etc.)
  - List authors should send live rando and kit list only to the independent team, in a protected manner
  - Independent biometrics team will perform the analysis using the IA programs which are previously developed by the blinded programmer, by replacing dummy lists with real data
  - Independent biometric team will share the results only with the data monitoring committee (DBC), in restricted folders

All the independent team activities should be well planned and described in SOP and IA charter

2. How to maintain the blinding?

ii. Avoid potentially unblinding data readiness before DBL/Unblind

ISSUE / CHALLENGE

Potentially unblinding data are measurements that are directly correlated to the treatment a subject had received.

Laboratory tests

- Anti-Drug Antibody, Target Engagement , Receptor Occupancy, Biomarker data, etc.
- PK data. If PK drug concentration are below the LoQ, then it is very likely the subject is on placebo treatment. Conversely, if high PK drug concentrations are measured, it indicates that the subject had been on active treatment.

Related side effects / related AE or SAE

- for example specific adverse events / adverse drug reactions / toxicities which are well know to be related to the investigational product. Related side effects or AE, are hardly to be blinded (ex. Vomiting, Diarrheal, injection site reactions, etc.) because are immediately evident to patients and investigators

2. How to maintain the blinding?

ii. Avoid potentially unblinding data readiness before DBL/Unblind

SOLUTIONS and ADEQUATE PROCEDURES

Laboratory tests

Potentially unblinding laboratory tests must be performed by an external laboratory.

Some reporting related activities have to be conducted before DBL/unblinding:

A. Some activities (SAS programming) must be performed before DBL/unblinding

B. DM cleaning are strategically planned before DBL/unblinding to be prepared and once the study is ended, have cleaned data ready in the shortest time.

C. PK, ADA and other biomarkers evaluation often needed at IA

2. How to maintain the blinding?

ii. Avoid potential unblinding data readiness before DBL/Unblind

SOLUTIONS and ADEQUATE PROCEDURES

Laboratory tests

A. SAS programming

Do not include result file with real assay results, rather use un-populated or dummy result field in the data. Use re-masked subject ID if needed when providing results files for programming in preparation for merging

B. DM cleaning

Delegate the on-going data cleaning of the results to the external lab. Study team DM should only reconcile the external data vs CRF data using header data; On-going data transfer to the study team DM should include only header data.

2. How to maintain the blinding?

ii. Avoid potential unblinding data readiness before DBL/Unblind

SOLUTIONS and ADEQUATE PROCEDURES

Laboratory tests

C. IA

Thoroughly evaluate whether unblinding data are absolutely needed.

Employ an independent biometrics team (statistician and programmer). Independent biometrics team should not be involved in any start-up tasks (SAP, set-up of programs, strategic decisions, etc.)

- IA ➔ At IA an independent biometrics team (statistician and programmer) should perform the analysis. Independent biometrics team should not be involved in any start-up tasks (SAP, set-up of programs, strategic decisions, etc.)
  - External lab should send live data only to the independent team, in a protected manner
  - Independent biometrics team will perform the analysis using the IA programs which are previously developed by the blinded programmer, by replacing dummy data with real data
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All the activities should be well planned and described in SOP and IA charter

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SOLUTIONS and ADEQUATE PROCEDURES

Related side effects / related AE or SAE

- Use open label strategies
- Use an equivalent drug for the controlled group

Any Questions?

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References

Main guidelines

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