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BLINDED STUDIES AND CHALLENGES
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ABSTRACT

Human behavior is influenced by what we know or believe. In research there is a particular risk of expectation influencing findings, most obviously when there is some subjectivity in assessment, leading to biased results. Blinding is used to try to eliminate such bias that can be caused intentionally or unintentionally if participants or the research team are aware of who is receiving an active or placebo treatment.

INTRODUCTION

Blinding means withholding which group each participant has been assigned to. Studies may use single-, double- or triple-blinding. Single-blinding occurs in many kinds of studies, but double- and triple-blinding are mainly used in medical research.

Single blinding

If participants know whether they were assigned to the treatment or control group, they might modify their behavior as a result, potentially changing their eventual outcome. In a single-blind experiment, participants do not know which group they have been placed in until after the experiment has finished.

Double blinding

A Double-blind study is one on which neither the participants nor the study staff know which participants are receiving the experimental treatment and which ones are receiving either a standard treatment or a placebo. These studies are performed so that neither the patients nor the doctor's expectations about the experimental drug can influence the outcome.

Triple-blinding

Although rarely implemented, triple-blind studies occur when group assignment is hidden not only from participants and administrators, but also from those tasked with analyzing the data after the experiment has concluded. Researchers may expect a certain outcome and analyze the data in different ways until they arrive at the outcome they expected, even if it is merely a result of chance.

Role of STAT Programming in Blinded Studies

In Clinical trial programming more often time Double blind studies are performed, and the challenges faced by the programming team are detailed below: To start these Double-Blind studies, 2 independent programming teams are formed. The first team is the Blinding team, where the programmers or Statisticians involved in it are blinded.

The other team is Un-Blinding team and are more often time are the external vendors outside of the organization. They are not part of the programming but are provided with original randomization file to un-blind the data by running programs created by Blinding team.

The programming part begins with Demographics data shared between Blinding team and Un-Blinding team.

Blinded Team	Un-Blinding Team
Dummy Randomization file will be provided by Clinical group to use in DM domain or Dummy treatments are assigned in ADSL programming using 1:1 randomization schema.	Unblinded team receives original Randomization file from Clinical group and replaces blinded treatment groups with original treatment groups in the ADSL program received from Blinded Group
Blinded team is responsible to create all SAS programs that generate datasets and outputs, and these same programs will be transferred to unblinded team.	After ADSL is re-created using original treatments, then re-run other ADAMs and TLFs. If they find any issues, they will reach out to blinded team to fix the issues.

Sample of Blinded output

Accounting of subjects: Safety set
Data cut-off date - 02MAR2019
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	Blinded 1	Blinded 2	Total
Number of subjects screened	4	3	7
Number of subjects randomized/enrolled	4	3	7
Number of subjects who withdrew prior to dosing	0	0	0
Number of subjects dosed	4 (100)	3 (100)	7 (100)
Number of subjects who completed treatment	0	0	0

NOTE 1: Numbers in parentheses are percentages.

Sample of UN-Blinded output

Accounting of subjects: Safety set
Data cut-off date - 02MAR2019
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	Study Treatment A 25mg	Study Treatment B 50mg	Total
Number of subjects screened	4	3	7
Number of subjects randomized/enrolled	3	2	5
Number of subjects who withdrew prior to dosing	0	0	0
Number of subjects dosed	3 (100)	2 (100)	5 (100)
Number of subjects who completed treatment	0	0	0

PROGRAMATIC CHALLENGES

- The programs created at the Blinded side also needed to be run on the Un-Blind environment without any issues. Major Challenge we come across is the operating system used at both ends. Below setup code is added to each program to make sure the code runs in all the environments like Windows, Unix, Linux etc.

```
data _null_;  
  if ("%sysscp"="WIN") then do;  
    put "Code is running outside Company setup";  
  end;  
  else do;  
    call execute("%include '/biostats/setup.sas'");  
  end;  
run;
```

- Treatment groups shouldn't be hardcoded to generate TLFs, instead dynamic programming needs to be implemented using TRT01P/TRT01A variables to make sure when unblinded team runs these programs original treatment groups are populated in outputs.

```
define col1 / display left "Blinded 1" width=14 spacing=4;
```

```
define col2 / display left "Blinded 2" width=14 spacing=4;
```

```
define col1 / display left "&trt1" width=12 spacing=1;
```

```
define col2 / display left "&trt2" width=13 spacing=1;
```

- Because of different operating systems, we must make sure the data is clean and no fuzzy data or invisible characters. Most of the times studies are Ongoing so anticipate fuzzy data and communicate with both programming teams.

UNIX/LINUX vs WINDOWS Operating Systems:

LBNAM:

Blinded team: UNIDADE LABORATÓRIO

Unblinding team: UNIDADE LABORATÓRIO

CMTRT:

Blinded team: SWEET COMBINATION

Unblinding team: SWEET COMBINATION

PACKAGE DETAILS FOR UNBLINDING TEAM

A Package is created at Blinded side and securely transferred online to the Unblinding team which is an external vendor. Here the package contains various folders with all the SDTM and ADAM datasets, programs, Outputs generated, and the macros used to run the programs. There is also a Handover document which mentions the contents of the package and a 'Read me' file which explains how to unblind the data by using original Randomization file.

Name	Date modified	Type	Size
STUDY_blinded	10/16/2023 7:38 PM	File folder	
STUDY_programs	10/16/2023 7:39 PM	File folder	
STUDY_SDtm_ADaM	10/16/2023 7:39 PM	File folder	
STUDY_specifications	10/16/2023 7:39 PM	File folder	
STUDY_support	10/16/2023 7:40 PM	File folder	
Company_macros	10/16/2023 7:40 PM	File folder	
STUDY DMC Handover Document	3/19/2021 6:26 PM	Microsoft Word D...	41 KB
STUDY_DMC_ReadMe	3/19/2021 6:34 PM	Microsoft Word D...	20 KB

Snippet of 'Read me' File

7. Create ADSL by merging the unblinded IXRS data (received separately) and update TRT01xx variables to represent the actual/planned treatment received by the subjects.

```
Proc Sort data=derived.&RANDOMIZATION_FILENAME out=RAND;
by SUBJID;
run;

Data ALL4;
merge ALL3(in=in_ALL1)
RAND(
  keep=SUBJID TRT01AN TRT01A STRATUM
  rename=(TRT01AN = _TRT01AN TRT01A = _TRT01A)
  in=in_RAND
);
by SUBJID;
drop _TRT01A _TRT01AN;
length TRT01A TRT01P $200;
if in_ALL1 and not in_RAND
then put 'WARN' 'ING:subject is in data but not in randomization file: ' _all_ ;
if in_ALL1 and in_RAND ;
TRT01AN = _TRT01AN;
TRT01A = _TRT01A;
Run;
```

8. After ADSL has been created, re-run ADaM datasets and TLF programs in any order. Each program should generate.LOG, LST and .RTF
9. Note that the data cut-off date is <20MAR2019> for this transfer (this was the date of

UNBLINDING PROCEDURE

- Unblinded team receives original Randomization file from the Clinical group and replaces blinded treatment groups with original treatment groups in ADSL.
- After ADSL is re-created using original treatments, then re-run other ADAMs and TLFs. If they find any issues, they will reach out to the blinded team to address the issues.
- Both teams work together and resolve any issues related to data or execution of programs.
- Once all the issues are resolved, the unblind team submits the original data along with re-created TLFs with original treatment groups to DMC for their review.

LESSONS LEARNT TO MAKE A SUCCESSFUL DELIVERABLE

- IDMC deliverables come with time constraints and tight timelines, so resource planning is always key.
- Making sure SDTM data is clean, Given the ongoing status of study always anticipate the data issues/dirty data and communicate well in advance to involved team members.
- Testing the programs on blinded data using dummy unblinded treatments, so that we can anticipate label lengths/page breaks/page shifts in outputs.
- Dry run with unblinded team and implementing their comments.

REFERENCES

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1118396/>

<https://www.slideshare.net/terryshaneyfelt7/blinding-in-clinical-trials-63673812>

<https://www.scribbr.com/methodology/double-blind-study/#:~:text=In%20a%20single%20blind%20study%2C%20only%20the%20participants%20are%20blinded,the%20researchers%20analyzing%20the%20data.>