

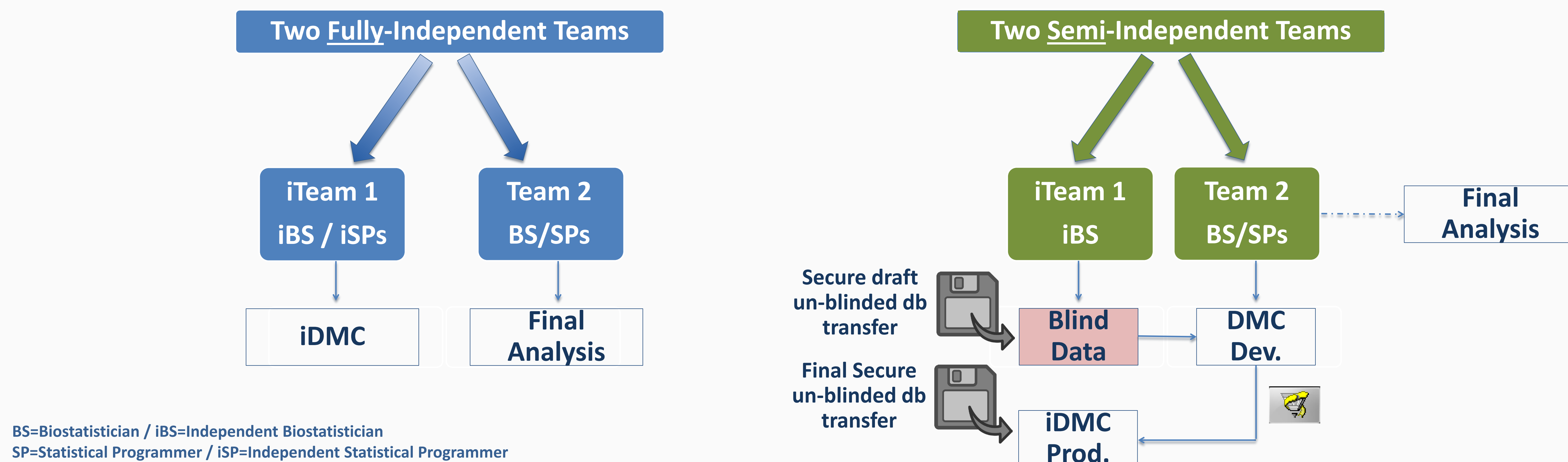
Blinding the un-Blinded

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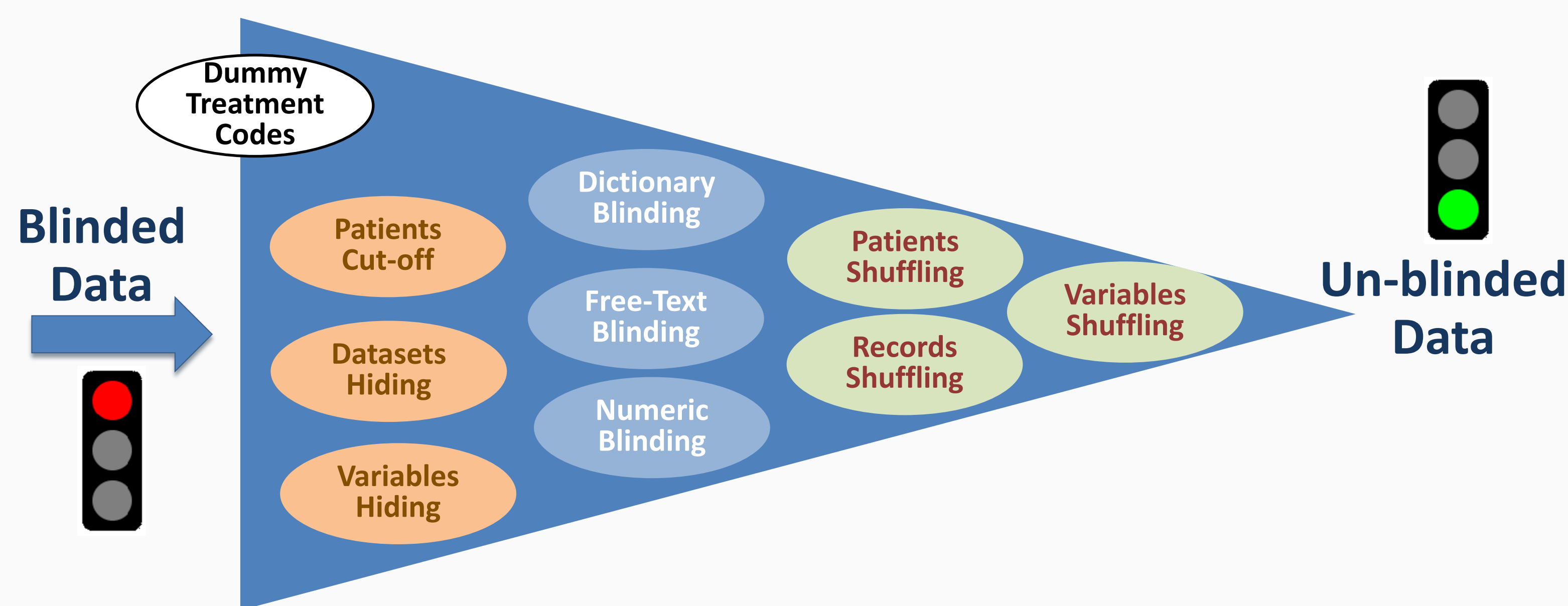
ABSTRACT

In blinded or confirmatory Open Label trials where independent analyses are required by a DMC during the course of the trial, rules should be defined so that blinding is not compromised and bias remains controlled; for these “interim” analyses separate teams are required. Analysis programs are developed by a blinded team using dummy codes then transferred to a separate area handled by the un-blinded team who runs programs with real treatment codes. Using dummy codes may be not enough, for example when drug relationship is specific to one arm or when a particular AE may lead to guessing the arm. In order to overcome this we developed a process so that data are blinded by applying systematic ‘data masking’ criteria like shuffling patients and/or records, free text and dictionary blinding. This approach can be also useful when developing mock-up outputs where the use of test/partial data is required; this way the programming team will be exposed to more ‘real’ data scenarios.

POSSIBLE OPTIONS WHEN BLINDED vs UN-BLINDED TEAMS ARE RECOMMENDED



BLINDING AND MASKING DATA PROCESS



Patients Cut-off a % of patients are selected

Datasets/Variables Hiding datasets and variables not needed may provide drug related information are removed

Dictionary Blinding i.e. get unique observed SOC/PTs and randomly assign one of the unique term to each occurred AE

Free Text Blinding free-text is replaced with a random set of characters i.e. XXXXXXXX

Patients Shuffling In all datasets patient id is systematically shuffled. Patient 001 may be assigned records of patient 002, etc.

Records Shuffling A number of records are randomly exchanged

Variables Shuffling For selected variables, expected values will be randomly assigned. For example if applied to drug relationship, and if expected values are “Not related” and “Related”, the original value will be randomly replaced with one of the two values

EFFECT OF BLINDING / MASKING

PATIENTS SHUFFLING

| WTABLE: Work.DemUnblinded | | | | | | |
|---------------------------|-----------|---------|-----------|-------------|-------|--------|
| | SUBJECTID | SITENUM | SITEGROUP | BRTHDR | AGEIC | SEX |
| 1 | 24892 | 272725 | ITALY | 13 JAN 1949 | 66 | Female |
| 2 | 25571 | 272731 | FRANCE | 17 JUN 1950 | 64 | Male |
| 3 | 25572 | 271372 | FRANCE | 12 SEP 1967 | 47 | Female |
| 4 | 25573 | 273345 | TURKEY | 18 MAY 1942 | 73 | Female |
| 5 | 25646 | 273012 | ITALY | 01 NOV 1950 | 64 | Male |
| 6 | 25671 | 272720 | FRANCE | 27 SEP 1936 | 78 | Male |
| 7 | 25800 | 273012 | FRANCE | 25 FEB 1972 | 43 | Male |
| 8 | 25999 | 272728 | ITALY | 03 OCT 1948 | 66 | Male |

Demography data for patient 24892 have been ‘exchanged’ with patient 26571

| VIEW TABLE: Work.DemUnblinded | | | | | | |
|-------------------------------|-----------|---------|----------------|-------------|-------|--------|
| | SUBJECTID | SITENUM | SITEGROUP | BRTHDR | AGEIC | SEX |
| 21 | 26458 | 272932 | PORTUGAL | 10 APR 1960 | 55 | Female |
| 22 | 26470 | 273382 | ITALY | 06 JAN 1940 | 75 | Male |
| 23 | 26571 | 273012 | ITALY | 13 JAN 1949 | 66 | Female |
| 24 | 26662 | 272012 | TURKEY | 18 MAY 1942 | 73 | Female |
| 25 | 26678 | 272731 | FRANCE | 17 JUN 1950 | 64 | Male |
| 26 | 26712 | 273349 | ITALY | 21 MAY 1966 | 49 | Male |
| 27 | 26720 | 272446 | UNITED KINGDOM | 18 DEC 1958 | 56 | Female |
| 28 | 26729 | 271367 | GERMANY | UN UNK 1975 | 39 | Male |

DICTIONARY BLINDING

| CM Class | CM PT Term | NBefore | Nafter |
|--|---------------------------|---------|--------|
| 5-HT3 ANTAGONISTS | GRANISETRON HYDROCHLORIDE | 245 | 41 |
| 5-HT3 ANTAGONISTS | ONDANSETRON | 12 | 51 |
| ANGIOTENSIN-CONVERTING ENZYME INHIBITORS | RAMIPRIL | 24 | 40 |
| ANTIHISTAMINES | CLEMASTINE | 18 | 26 |
| BETA-ADRENOCEPTOR BLOCKING AGENTS | BISOPROLOL FUMARATE | 23 | 45 |
| CALCIUM CHANNEL BLOCKING AGENTS | AMLODIPINE | 16 | 48 |
| HERBAL HOMEOPATHIC & DIETARY SUPPLEMENTS | IGNATIA | 16 | 35 |
| STATINS | SIMVASTATIN | 14 | 40 |
| STEROIDS | DEXAMETHASONE | 18 | 40 |
| THYROID HORMONES | LEVOTHYROXINE SODIUM | 16 | 47 |
| | | 13 | 42 |

%BLINDATA + multiple-sheets XLS file with blinding specifications

%BLINDATA(FILE=..\Metadata\Input\Sponsor_Study_Blindata.xls)

Cover_Page General_Criteria General_Specification Datasets Remove

| Parameter | Description | Value |
|----------------|---|--|
| RAWUN | Unblinded datasets location | ..\DMC\Blind\Biostatistics\Uninputdata\Raw\Unblinded |
| RAWBLIND | Blinded datasets location. This will contain the artifacted datasets (derived from RAWUN) | ..\DMC\Blind\Biostatistics\Uninputdata\Raw\Blinded |
| REMOVEDS | List of datasets that regardless of the data artifact process should be not provided to blinded team | See assessment in Datasets sheet |
| REMOVEVARS | YES/NO (default=NO). If YES specify in Remove_Vars sheet variables to be removed from each raw datasets | YES |
| REMOVEVARSAALL | List of variables to be removed from all datasets | SUBJECT SITEID SITE |
| PTSHUFFLE | % of patients to be included (default=100% so no out will be applied all extracted patients will be provided to blinded | 100 |
| RECSHUFFLE | YES/NO See General Criteria (default=YES). If YES specify additional criteria in Records_Shuffle sheet | YES |
| NUMBLIND | YES/NO See General Criteria (default=YES). If YES specify additional criteria in Numeric_Blinding sheet | NO |
| TXBLIND | YES/NO See General Criteria (default=YES). If YES specify additional criteria in Text_Blinding sheet | YES |
| DICTBLIND | YES/NO See General Criteria (default=YES). If YES specify additional criteria in Dictionary_Blinding sheet | YES |
| VARSHUFFLE | YES/NO See General Criteria (default=YES). If YES specify additional criteria in Variables_Shuffle sheet | YES |
| DSPT | Datasets identifying patients e.g. DM | PTID |
| SUBID | Subject Id | SUBJECTID |

| Dataset Name | Variables |
|--------------|--|
| RAND | TXARM TXARMV COHRT |
| AEDE | AELLT AELLTCD AEPTCD AEHLT AEHLTCD AEHLGTCD AESOCCD RDTF |
| | TXAD1 TXAD1_RAW TXADU1 TX1D TX1DR TX1DT TX1TM TX1MU1 TX1MU2_RAW ROUTE1 |
| | ROUTE1V TXFRQ1 TXFRQ1V LOT1 |
| | TXAD2 TXAD2_RAW TXADU2 TX2D TX2DR TX2DT TX2TM TX2MU2 TX2MU2_RAW ROUTE2 |
| | ROUTE2V TXFRQ2 TXFRQ2V LOT2 |
| | SRDET1 SRDET2 SRDET3 SRDET4 SRDET4V SRDET4 SRDET5V |

| Dataset Name | VERBATIM_V Variable | PT_DECODE_V Variable | SOC_CLASS_V Variable |
|--------------|---------------------|----------------------|----------------------|
| AEDE | AERAW | AEDECOD | AESOC |
| MD1 | MDRAW | CMDECOD | CMCLAS |

If some CMs are typically related to the experimental drug, although using dummy treatment arms we may still see an higher incidence of those particular CMs expected for the experimental drug thus making some conclusions on the safety profile of the experimental drug. By blinding the dictionary, we will still report the same observed type of CM Class/PT but with a ‘modified’ incidence rate.

CONCLUSIONS

- Reduced use of resources (no team duplication) and improve re-usability of DMC Analysis Programs for Final Analysis
- The same developing team is used, thus owning the programming package for all analysis-tasks
- The %BLINDATA solution only requires the specification of a number of parameters to correctly apply the ‘blinding/masking’ criteria