

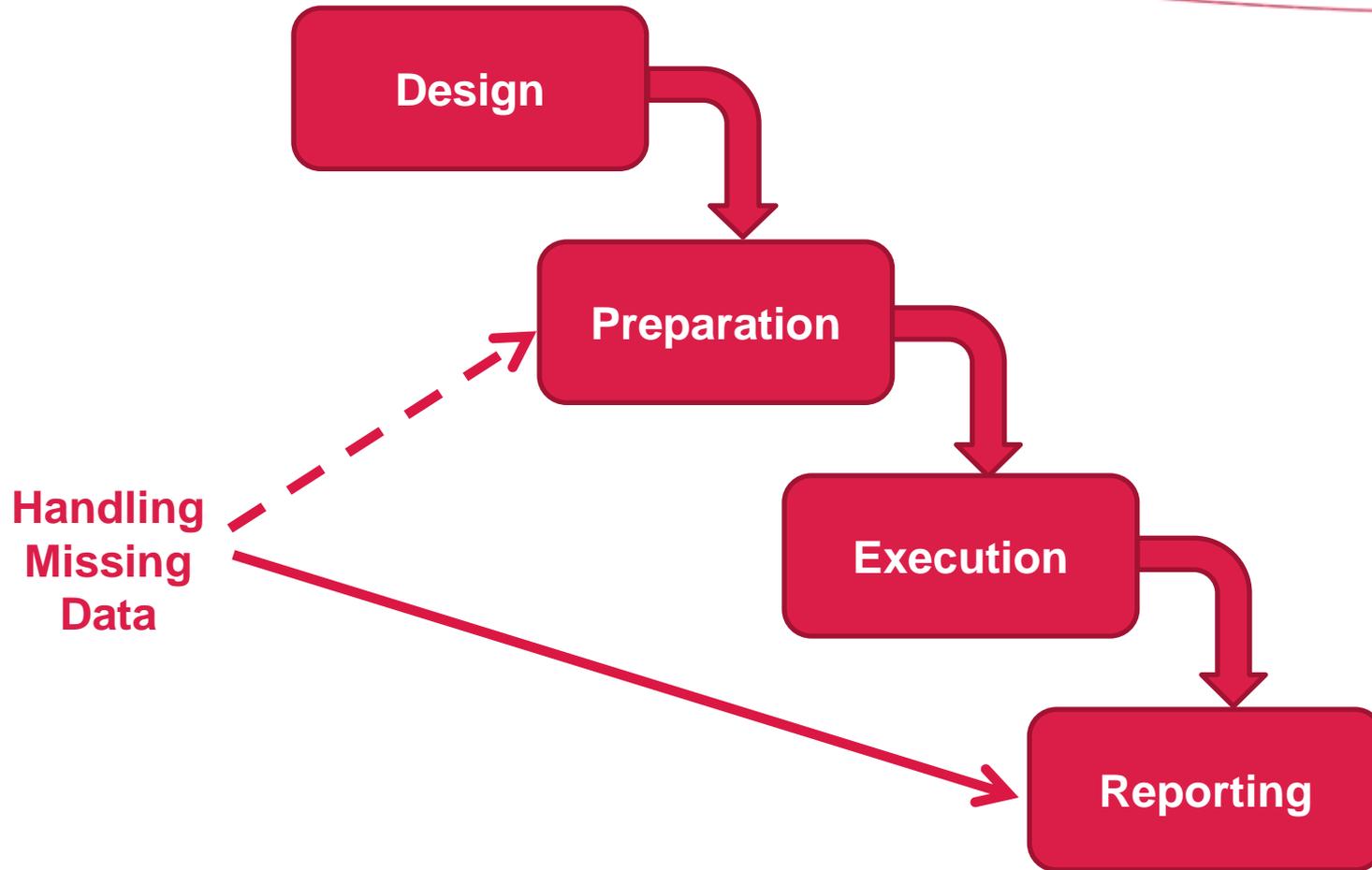


Practical Approaches to Minimising Missing Data

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When do we start thinking about missing data?



How does Missing Data occur?

Assessment not done / result not available

- Technical problems
- Practical reasons why assessment cannot be done
- Results not documented / entered

Patient drops out of the study

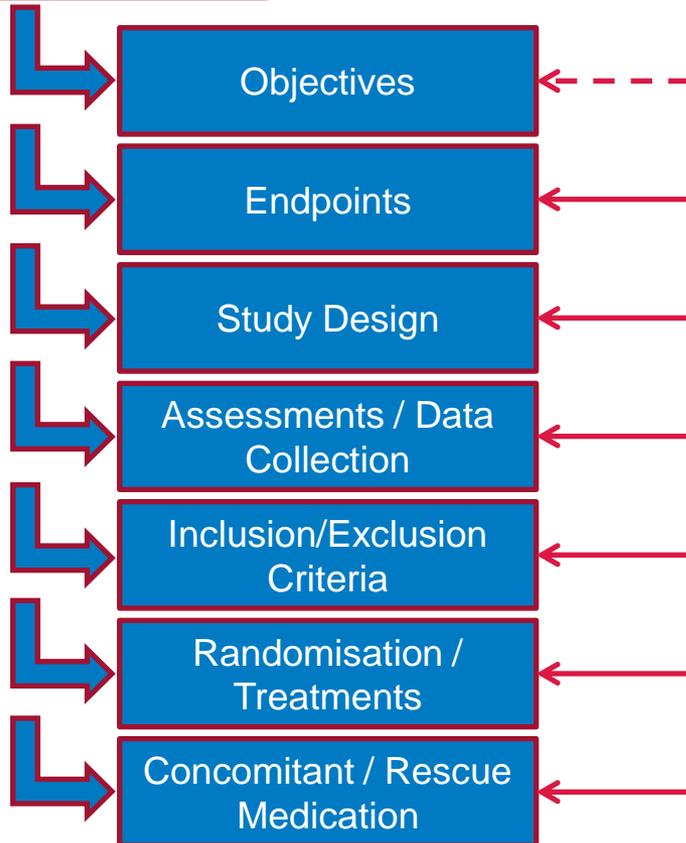
- Could be before or after randomisation
- Withdrawal of consent / unwilling to take study medication
- Adverse side effects / lack of efficacy

Patient misses visit

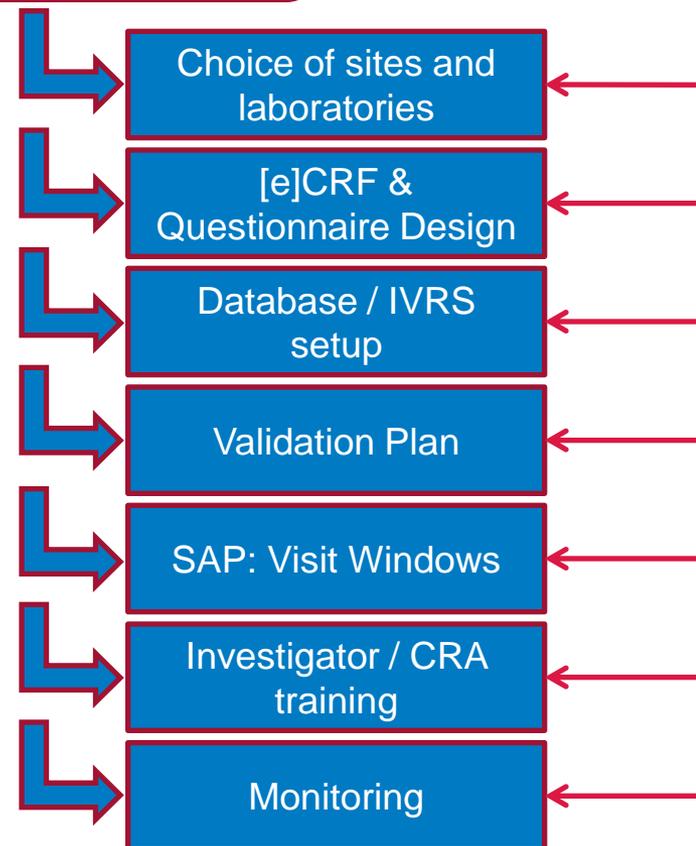
- Medical or practical reasons

When should we start thinking about missing data?

Design



Preparation



Choice of Endpoint

Example: Diagnosis of Deep Venous Thrombosis

Regulatory requirements:

- CHMP Guideline (“prophylaxis of high intra- and post-operative venous thromboembolic risk”)
- Mandates use of bilateral venogram (“gold standard”)

Problem: patient compliance

- Invasive procedure, needs to be performed twice
- Patients often unwilling to comply
- Typically 20-30% of patients with incomplete or missing information

Learning points:

- Accepted endpoints may lead to systematically missing data
- Can regulators be influenced to accept different endpoints (radiography)?
- Possible alternatives (symptomatic events) require more patients



MNAR? MAR?
MCAR?

Assessment of Endpoint

Censoring of time-to-event endpoints

Limited time window for observation of outcome

- Survival / time to progression etc. → follow up to end of study
- Skin Bleeding Time (time until bleeding of inflicted injury stops) → typically 30 minutes observation time

Observed times may fall outside the window

- Concomitant anticoagulants (aspirin) may impact SBT
- Results in right-censored observations

Learning points:

- When observation times have to be limited, carefully consider time allowed
- Build flexibility into the protocol; observe emerging data



Study Design

Study Design influences drop-out rate

Design options:

- Parallel group, cross-over
- Enriched Enrolment and Randomised Withdrawal
- Placebo run-in period

Considerations:

- Higher order cross-over studies need fewer patients, but are more prone to drop-out (?), especially with invasive assessments
- Different designs answer different questions (EERW versus parallel group)
- Placebo run-in can be used to identify compliant patients
 - Unethical [Senn (1997)]
 - Doesn't work! [Davis et al (1995)]



MNAR?

Frequency & Intensity of Assessments

Several questionnaire-based endpoints

- Efficacy, Quality of Life
- Repeated assessment throughout the study
- Utilises telephone (IVRS) system for data collection

Problem: poor patient compliance

- ~20 minute phone call to complete questionnaires
- High burden on patients → unwillingness to participate

Learning points:

- Simplify study assessments
- Develop new instruments to measure outcomes



Inclusion / Exclusion Criteria

Study phase transition

- Randomised double-blind trial, followed by open-label extension
- Patients had to meet criteria to take part in extension

Problem:

- Some patients realised they would not be admitted to extension
- Patients did not see the value of participating in double-blind phase
- “Study procedures too cumbersome”

Learning points:

- Patients should know in advance what to expect
- Educate patients about impact of withdrawal on study outcome
- Keep study procedures simple



Treatments and Randomisation Procedure

Active treatment versus standard of care

- Open-label study
- Patients may have a-priori preference

Problem:

- Patients may withdraw between randomisation and first treatment

Learning points:

- Preferably conduct study as double-blind
- State order of events clearly in protocol
- Educate site staff, ensure patients aware of possible side effects
- Ask sites to minimise time between randomisation & application



Treatments and Randomisation Procedure

Two different approaches in two different protocols:

Prior to topical anaesthetic (if applicable):

- Inclusion/ Exclusion criteria evaluation
- Adverse events check
- Concomitant medication
- Randomization ←
- Dermal assessment and identification of painful area
- Physical examination including foot examination
- Vital signs (within 15 minutes before topical anesthetic)
- Pregnancy test
- Neurological examination including UENS and sensory function testing
- BPI-DN (questions 1, 3, 4, 5, 6, 8 and 9) will be recorded by subject
- EQ-5D and Norfolk to be completed by subject

Treatments and Randomisation Procedure

...versus:

Prior to topical anaesthetic:

- Inclusion/ exclusion criteria evaluation
- Adverse events check
- Concomitant medication
- Dermal assessment and identification of painful area
- Physical examination and sensory function testing
- Vital signs (within 15 minutes before topical anaesthetic)
- Pregnancy test (only women of childbearing potential)
- BPI-DN (questions 5 and 9F) will be recorded daily by subject during the study
- 'Pain now' score to be completed by subject
- EQ-5D and HADS to be completed by subject
- Self-Assessment of Treatment questionnaire (SAT) to be completed by subject
- Randomization 

Concomitant / Rescue Medication

Rescue medication can prevent patient drop-out

- Relief of symptoms, usually related to target indication

Example:

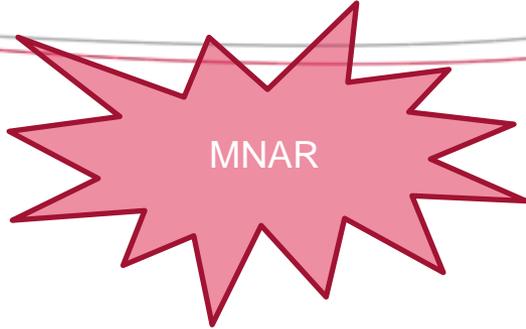
- In psoriasis, allow low dose steroids for difficult to treat areas
- Not likely to affect overall assessment of efficacy

Problem in other indications:

- Effect of rescue medication may mask the true effect of study medication
- In proof of concept studies, this may not be appropriate

Learning points:

- May want to regard use of rescue medication as an efficacy endpoint
- Analyse time to rescue medication (Kaplan-Meier)



MNAR

Choice of Laboratory: Local versus Central

Central laboratory:

- Facilitates data tracking and cleaning
- Easy to plan, consistency between countries

Local laboratories:

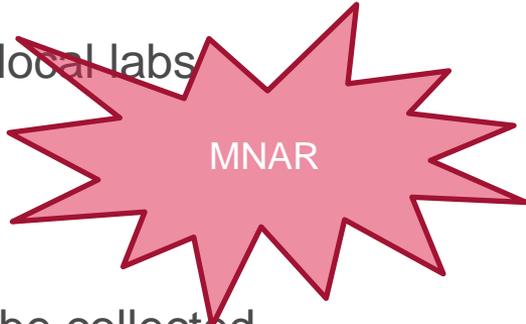
- Often used aside central lab, for unexpected events, SAEs

Problem:

- Database/CRF may not be set up to collect unscheduled local labs
- Data from local labs may not be included in TLFs

Learning points:

- Consider in advance whether results from local labs may be collected
- If yes, think about flexibility in data collection



MNAR

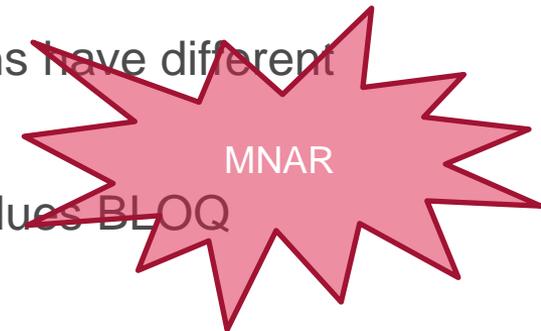
Choice of Laboratory: Assay Performance

Limit of quantification of laboratory measurements

- Different assays have different detection limits
- Values below the limit (BLOQ) are right-censored

Example: d-dimer

- Protein fragments in the blood after degradation of blood clot
- Several assays commercially available, using different antibodies
- Limit of quantification may differ → censored observations have different meaning
- Using the wrong assay may lead to high proportion of values BLOQ



Learning points:

- For local labs, ensure standardisation across sites
- For central lab, make sure you know what assay will be used

eCRF Design / Validation Plan

Example: Phase 1 PK Study

- Multiple measurements on PK in plasma and urine
- Actual sampling times collected on eCRF

Problem: mismatch between sampling times and concentrations

- Noticed during reconciliation
- Site had accidentally deleted a page with sampling times

Learning points:

- Perform regular reconciliations
- Modify eCRF so site can't delete a whole page by mistake



Other Considerations – Informed Consent

Typical informed consent:

Participation in this study is entirely voluntary. Your treatment and your doctor's attitude toward you will not be affected should you decide not to participate in this study... You will be asked to return for follow-up visits and to provide follow-up information... If you agree to participate, you may withdraw from the study at any time without affecting any benefits to which you would otherwise be entitled.

Alternative:

Participation in this study is entirely voluntary. Your treatment and your doctor's attitude toward you will not be affected should you decide not to participate in this study... You will be asked to return for follow-up visits and to provide follow-up information *even if you have stopped taking study medication. Your doctor will contact you to obtain follow-up information.* If you agree to participate, you may withdraw from the study at any time without affecting any benefits to which you would otherwise be entitled.

[Wittes (2009)]

Other Considerations – Discontinuations

Definition and use of “discontinuation” in study protocol:

- Typically, no distinction between discontinuation of medication, and discontinuation from the study
- “... subject ceases participation in the study ...”

Alternative:

A discontinuation from study medication occurs when a participant permanently stops taking study medication. A discontinuation from the study occurs when a participant in the study dies, is permanently lost to follow-up, or withdraws consent, regardless of the circumstances, prior to completion of the protocol.

[Wittes (2009)]

And finally...

Other suggestions to minimise missing data:

- Don't do the study, or don't collect any data for the study
 - Although perhaps that means all data is missing rather than none
- Make up the data
 - This has been tried
 - Risks imprisonment and other inconveniences

Personal conclusions

- “Prevention is better than cure”
- Prevention of missing data requires thought at all stages:
 - Study design, planning, execution, reporting
- Keep missing data in mind at all times
- General rule: keep it simple

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References

- Cleland JGF, Torp-Pedersen C, Coletta AP, Lammiman MJ (2004) : “A method to reduce loss to follow-up in clinical trials: informed, withdrawal of consent”. The European Journal of Heart Failure 6:1–2
- Davis CE, Applegate WB, Gordon DJ, Curtis RC, McCormick M (1995): “An empirical evaluation of the placebo run-in”. Control Clin Trials 16(1):41-50
- Fleming TR (2011): “Addressing Missing Data in Clinical Trials”. Ann Intern Med. 154:113-117
- Senn S (1997): “Are placebo run ins justified?” BMJ 314:1191
- Wittes J (2009): “Missing Inaction: Preventing Missing Outcome Data in Randomized Clinical Trials”. Journal of Biopharmaceutical Statistics, 19: 957–968