Modern Approaches to Handling Missing Data in Clinical Trials

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Outline

- Missing data in trials – the problem
- Ad hoc approaches
- Framework for analysis
- Multiple imputation
- Sensitivity analysis
- Summary

Missing data

- Values that are not available but would have been meaningful for analysis had they been observed. Reasons could include:
  - participant withdrawal
  - loss to follow-up
  - skipped appointments/tests/questions
  - data lost accidentally
- Whether data are meaningful for analysis depends on what's being estimated – e.g. treatment effect in all randomised or compliers only
- Vast majority of trials have at least some missing data

Missing data – the problem

- Untestable assumptions must be made about the missing data – getting this wrong can lead to bias
- Reduced power compared to an analysis with complete data
- Reduced generalisability
- Ultimately can lead to inappropriate conclusions

⇒ **Try to prevent missing data in the first place!**

Another problem: common use of inappropriate methods of analysis

Complete case analysis

ID	Weight t1	Weight t2
1	76	.
2	79	86
3	60	60
4	54	.
5	91	94

- Assumes participants with complete data representative of those with missing data – can lead to bias if assumption wrong
- Not recommended for longitudinal data as inefficient
- Can be OK for outcomes measured at a single time point if analyses adjusted for baseline predictors of the outcome and missing data

⇒ *Think about associations with missing data when specifying covariates for adjustment*

Last observation carried forward

ID	Weight t1	Weight t2
1	76	.
2	79	86
3	60	60
4	54	.
5	91	94

Last observation carried forward

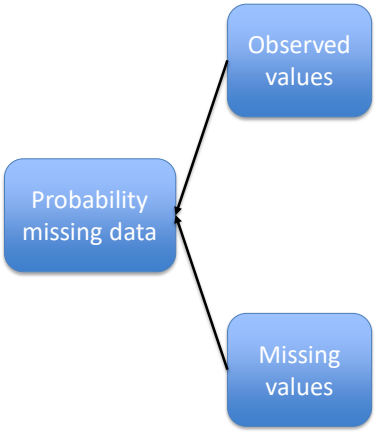
ID	Weight t1	Weight t2
1	76	**76**
2	79	86
3	60	60
4	54	**54**
5	91	94

- Assumes outcomes do not change after dropout – unrealistic in many settings
- Replaced values analysed as if they were observed, which fails to account for uncertainty due to missing data
- Widely condemned in the trials literature
- Many journals recommend avoiding the method, e.g. JAMA

Better approach

- Start with a sensible assumption about the cause(s) of missing data – good data collection and clinical input important
- Choose a statistical method that produces valid results under this assumption
  - unbiased estimates of the treatment effect and its standard error
  - efficient, i.e. makes the best use of the observed data
- Investigate the sensitivity of conclusions to the assumption made about the missing data
- Report on all of this – state and justify the assumptions made

Missing data assumptions



Missing completely at random
Probability missing data does not depend on observed or missing values, *e.g. data forms accidentally lost*

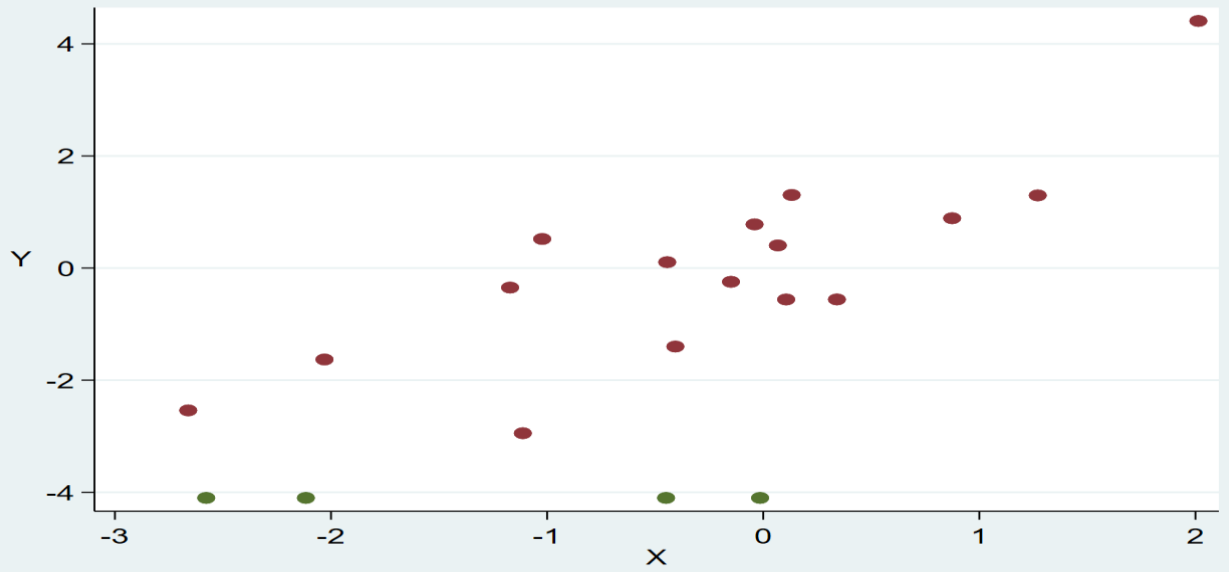
Missing at random
Probability missing data depends on observed but not on missing values, *e.g. those with a higher recorded baseline weight more likely to dropout*

Missing not at random
Probability missing data also depends on the values of the missing data, *e.g. subject skips the assessment because they've gained too much weight*

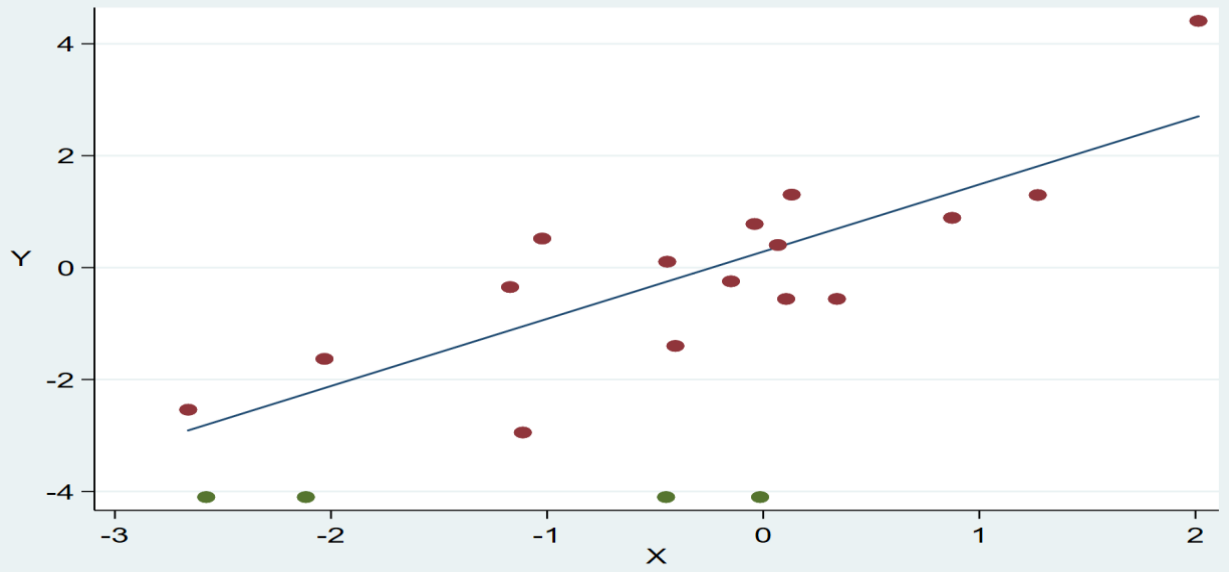
Missing at random

- Sensible starting assumption for the analysis of many clinical trials
- More realistic than the stricter missing completely at random assumption
- Statistical methods that produce appropriate results under a missing at random assumption include:
  - maximum likelihood methods, e.g. mixed models
  - inverse probability weighting
  - multiple imputation

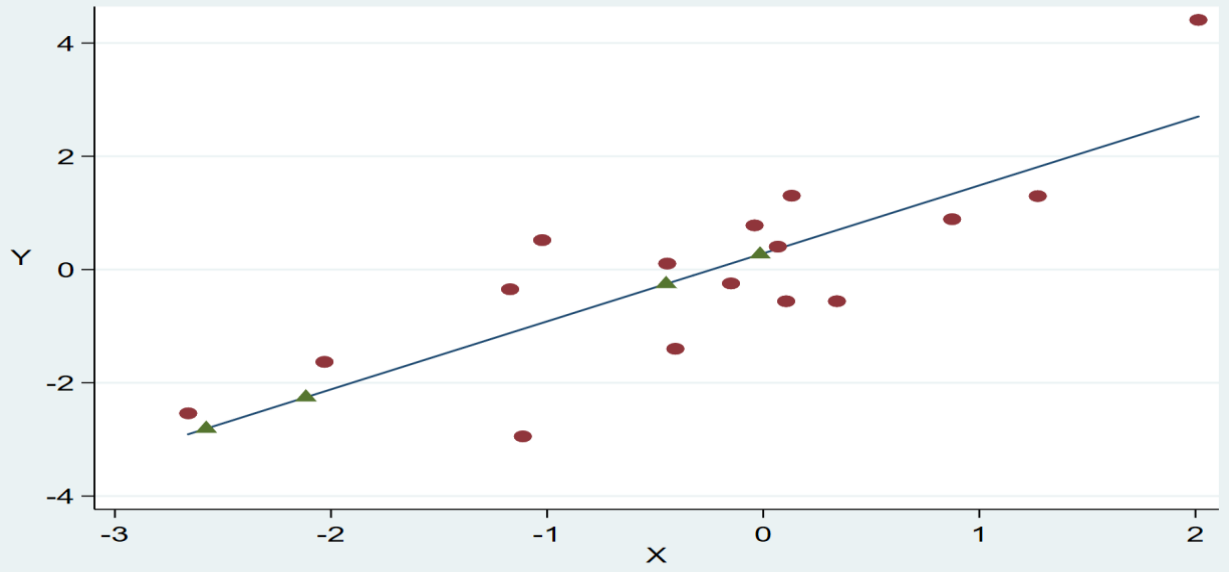
Regression example



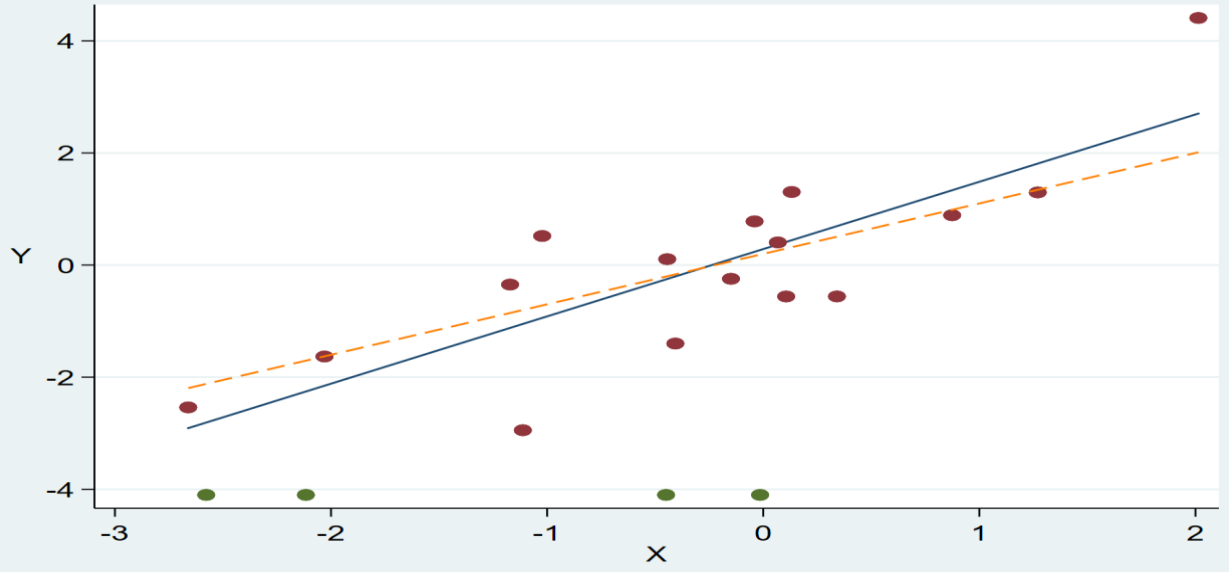
Regression example



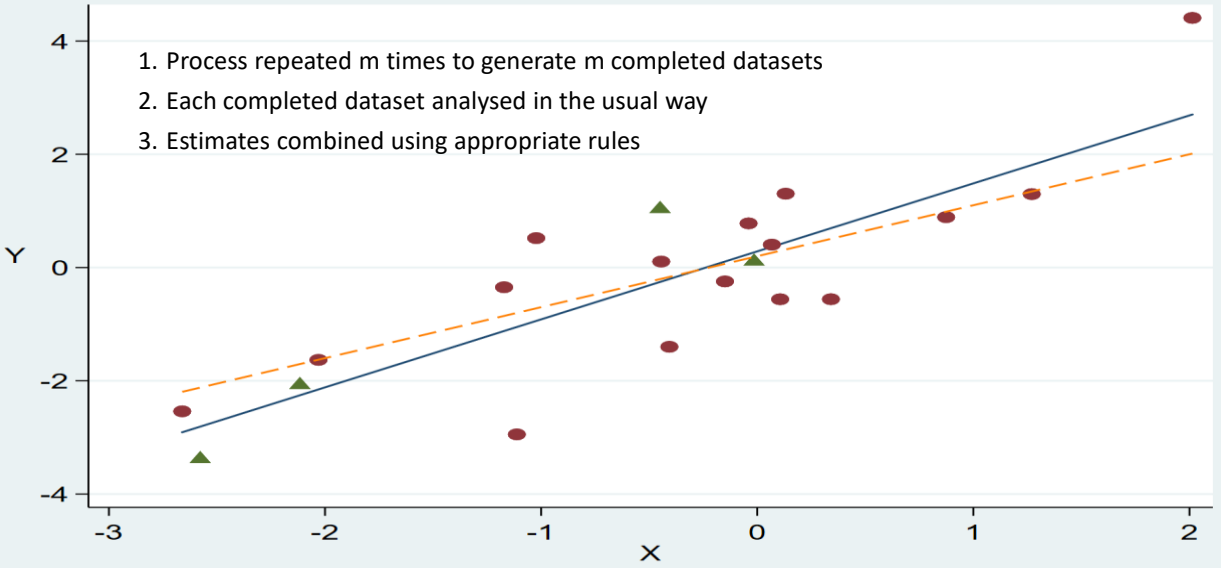
Regression example



Multiple imputation



Multiple imputation



Multiple imputation

- Increasingly popular in trials due to its flexibility – can be used with any intended analysis model
- Great for sensitivity analyses
- Can benefit from the inclusion of auxiliary variables:
  - not a part of the analysis model but included in the imputation model to improve the prediction of missing values
  - want variables associated with the outcome (precision gains) or both the outcome and the probability of missing data on the outcome (bias reduction)
  - baseline or post-randomisation

⇒ *Think about potential auxiliary variables when designing a trial*

MI by treatment group

- If possible, better to fit separate & identical imputation models to each treatment group:
  - easier to specify
  - facilitates subgroup analyses for any baseline characteristic included in the imputation model
  - produces unbiased average treatment effects when subgroup analyses not of interest
  - allows for unequal variances between treatment groups
  - not much lost precision when there is no effect modification

Sensitivity analysis

- See how results change under alternative plausible assumptions about the missing data
- Alternative assumptions should contradict the main assumption
  - wouldn't use complete case analysis as a sensitivity analysis to multiple imputation
- For primary analysis under a missing at random assumption, consider missing not at random assumptions

Pattern mixture models

- Let δ = mean difference in weight at final time point between missing and observed values
  - missing at random: conditional on observed data, δ = 0
  - missing not at random: conditional on observed data, δ ≠ 0
- Specify plausible values for δ and vary between treatment groups

Analysis	Assumption	δ intervention group	δ control group
Primary	MAR	0	0
Sensitivity 1	MNAR	+5kg	0
Sensitivity 2	MNAR	0	+5kg
Sensitivity 3	MNAR	+5kg	+5kg

- Multiple imputation: just add δ to the imputed values!

Summary

- Prevent missing data in the first place
- Start with a sensible assumption about the missing data and choose an analysis method valid under this assumption
- Missing at random often reasonable – maximum likelihood methods, inverse probability weighting and multiple imputation
- Collect information to support the analysis – e.g. reasons for missing data and auxiliary variables
- Conduct sensitivity analyses

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