Sensitivity analysis for not-at-random missing data in trial-based cost-effectiveness analysis using multiple imputation

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Missing data are common in RCTs
  → Loss of power
  → Risk of bias

Particularly important in CEA
  - Complex data
  - Long term follow-up

Typically assume data are "missing at random"

But risk of being missing could depend on the data value itself → MNAR
**MAR**: Missingness only depends of observed variables
- Can get valid inference using the observed data

**MNAR**: missingness depends of outcome value itself
- E.g. less likely to complete a health questionnaire when ill
  - Cannot judge from the data
  - Need additional assumptions to conduct the analysis

But often plausible

Guidelines → Should assess whether results robust to MNAR assumptions

Clear gap between recommendations and practice

Recommendation 15: Sensitivity analyses should be part of the primary reporting of findings from clinical trials. Examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting.  
*(NRC 2010)*
Pattern-mixture models (PMM) are one possible approach for MNAR analysis.

Distribution = *mixture* of observed and missing distributions.

For example: assuming missing and observed data have same distribution, but with mean shifted by \( \delta \)

\[ Y_{\text{miss}} = Y_{\text{obs}} + \delta \]

\( \delta \) = average difference between missing and observed values (conditionally on observed data)

Can also use a multiplicative factor \( c \):

\[ Y_{\text{miss}} = Y_{\text{obs}} \times c \]
Multiple Imputation (MI) commonly used in trial-based CEA

Typically under MAR, but can accommodate MNAR

Idea is simple:
1. Conduct usual MI
   - Under MAR
2. Modify imputed data to reflect MNAR assumption
   - e.g. reduce imputed data by 10%
3. Analyse as usual MI dataset
   - Using Rubin’s rules

Sensitivity analysis can be conducted over a range of plausible values for $\delta$, to see how affect conclusions
Example: the 10 Top Tips trial

- RCT, evaluating a brief intervention for weight loss, in UK general practices
- **Primary outcome**: weight loss at 3 months
- **Follow-up**: 2 years (3, 6, 12, 18, 24 months)
- **CEA**:
  - Costs: NHS resource use over 2 years
  - Effectiveness: EQ-5D at each visit → QALYs over 2 years

- N=537 patients
- But only 60% at 24M, and 30% complete cost-effectiveness data
- More likely to drop out if less successful → MNAR
Applying **PMM** approach to 10TT:

- Let’s denote \( c = \text{MNAR multiplicative parameter for the QoL scores} \)
  
e.g. \( c = 0.9 \): the missing QoL are assumed 10% lower than under MAR

- What values for \( c \)?
  
  - \( c = \{1, 0.95, 0.90\} \) (= drop out probably worst off, somewhere between MAR, and 10% worst)
  
  - \( c \) could differ between arms, but more likely to be close to each other

  → 7 scenarios considered
→ Under MAR, 48% probability 10TT cost-effective
→ But results sensitive to departure from MAR
Discussion

- Easy to implement
- Results can be sensitive (not always the case!)
- Challenges:
  - Choosing sensitivity parameters
    - Expert opinion
    - Tipping-point
  - Reporting
    - Clarity is essential
  - Alternative: reference-based imputation
Can never recover missing information ⇒ avoiding missing data best solution

Missing data → make assumptions → what if do not hold?

Multiple imputation offers a convenient way to conduct these sensitivity analyses

Some challenges: elicitation, reporting, etc.
⇒ But not excuses not to conduct them

Likely will evolve over time, as become more routinely conducted
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