To impute or not to impute?

A comparison of statistical approaches for analysing missing longitudinal patient reported outcome data in randomised controlled trials

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Patient reported outcome measures

- Capture patients’ perceptions of pain/ function/ symptoms/ quality of life etc.
- Are increasingly used in clinical research
- May be more susceptible to be missing
Impact of missing data

- Loss of power
- Can introduce bias into the study results
  - Strong assumptions associated with analysis of incomplete data
- The use of inappropriate assumptions can lead to biased results
- Healthcare decisions need to be based on robust trial results
Aim of this presentation:

• Compare different approaches for handling missing longitudinal data
  • Maximum likelihood (ML)
  • Multiple imputation (MI)
  • Inverse probability weighting (IPW)
The Knee Arthroscopy Trial (KAT)

- Patellar resurfacing vs. no patellar resurfacing during knee replacement
- 1717 participants were randomised
  - 983 used in the simulation study
- Primary endpoint: Oxford Knee Score
  - SF-12 and EQ-5D-3L also collected
- Follow-up: at 3 months and yearly to 5 years
Design of the simulation study

- Sample without replacement (100, 250, 500, 750, ~1,000 observations)
- Impose longitudinal MAR data for 10%, 20%, 30%, 40%, 50%, 60% of participants
- Apply the three different analysis approaches: ML, MI and IPW
- Save treatment effects and their SEs
- Repeat for 1,000 simulations
- Calculate performance estimators (e.g. RMSE, MAE)
Methods

- Analysis model: multilevel mixed-effects model using ML
- Handle missing data by:
  - ML
    - No further adjustments to analysis model
  - MI
    - Missing data are imputed based on the MI model
  - IPW
    - Observations are weighted by the inverse of their probability of having complete follow-up data
Results

10% MAR

20% MAR

30% MAR

40% MAR

50% MAR

60% MAR

RMSE (treatment coefficient)

Sample size (simulation dataset)

ML  -  MI  -  IPW
Standard errors observed
Using additional PROMs data in the MI and IPW models
Conclusions

- Handling longitudinal PROMs with some missing outcome data
  - IPW is not recommended
  - ML and MI can perform similarly
  - MI outperforms ML if additional post-randomisation data can be utilised
Thank you..

• ..to my supervisors:
  – Professor Alastair Gray
  – Associate Professor Oliver Rivero-Arias
  – Professor Crispin Jenkinson

• ..to my funder:
  – The Medical Research Council

• ..to Professor David Murray and the KAT study team for access to the KAT data
References


Observed missing data patterns (Longitudinal simulation study)

<table>
<thead>
<tr>
<th>Missingness pattern</th>
<th>Total</th>
<th>True %</th>
<th>% used in simulation</th>
<th>Cumulative %</th>
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<tbody>
<tr>
<td>No follow-up data available</td>
<td>62</td>
<td>13.51%</td>
<td>22.06%</td>
<td>22.06%</td>
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<tr>
<td>Only three month data missing</td>
<td>49</td>
<td>10.68%</td>
<td>17.44%</td>
<td>39.50%</td>
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<tr>
<td>Only five year data missing</td>
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<td>10.02%</td>
<td>16.37%</td>
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<td>8.19%</td>
<td>85.41%</td>
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<tr>
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<td>4.79%</td>
<td>7.83%</td>
<td>93.24%</td>
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<tr>
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<td>4.14%</td>
<td>6.76%</td>
<td>100.00%</td>
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</tbody>
</table>
mixed oks i.comp_b_alloc oks_bl ///
   b100i.time i.sex age ///
|| id: time , ///
mle  cov(unstructured) stddev

The same model is applied to the missing data (ML approach):
mixed miss_oks i.comp_b_alloc oks_bl ///
b100i.time i.sex age ///
|| id: time , ///
mle  cov(unstructured) stddev
mi impute chained (pmm, knn(1)) ///
miss_oks25 miss_oks100 miss_oks200 ///
miss_oks300 miss_oks400 miss_oks500 = ///
i.comp_b_alloc oks_bl age i.sex ///
bmi i.ASAGrade i.site_size ///
i.OpComp_sim i.AlloProc, ///
add(`miss_perc') by(comp_b_alloc)

mi reshape long miss_oks, i(id) j(time)

mi estimate, post: ///
mixed miss_oks i.comp_b_alloc oks_bl ///
b100i.time i.sex age ///
|| id: time , mle  cov(unstructured)
logit full_fup oks_bl age i.sex bmi //
i.ASAGrade i.site_size i.OpComp_sim i.AlloProc

predict pr
gen ipw = 1/pr
reshape long miss_oks, i(id) j(time)
drop if full_fup == 0
mixed miss_oks i.comp_b_alloc

oks_bl b100i.time i.sex age || id: time , ///
    mle cov(unstructured) stddev pweight(ipw)
Best practice

“First, the single best approach [to handling missing data] is to prospectively prevent missing data occurrence.”