Trial participant attrition: implications for the evaluation of internet interventions for addictive behaviours

Dr. Matthijs Blankers

Arkin Mental Health Care, Amsterdam
Trimbos-institute, Netherlands Institute of Mental Health and Addiction, Utrecht
Academic Medical Centre, University of Amsterdam
The Netherlands

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Program

- Introduction
- Alcohol study (approaches to attrition)
- Smoking cessation study (appr. differential attrition)
- Discussion
Introduction
Attrition

- Attrition common in internet-based alcohol/tobacco trials
  - Alcohol: 22% (14 studies, Riper et al 2014)
  - Tobacco: 51% (22 studies, Civljak et al 2013)

- … this is often higher than in “land-based” trials
  - Alcohol: Kaner et al 2007: ~20%
  - Tobacco: Lancaster et al 2008: ~20%

- Should be prevented at all costs!
  - Brief follow-ups
  - Contact via email, phone,
  - Remuneration

- … however will occur
Attrition

- Consequences missing (outcome) data due to attrition:
  – May be selective and lead to biased effect estimates
  – Reduced power
  – ITT / analytical approaches require complete data

– Especially problematic when degree of attrition differs between trial arms (differential attrition) (Crutzen et al. 2015)

– Av. 18% attrition in health behavior change trials
  – 10% more attrition in intervention arms (Crutzen et al. 2015)
Questions

1. How to handle trial participant attrition?

2. What to do about differential attrition?

– Focus on imputation-based approaches

– Results of 2 studies presented:
  – 1. using alcohol intervention trial data
  – 2. using smoking cessation trial data
### Possible approaches

1. **Remove all cases/participants with missing outcome data**
   - complete cases analysis
   - Prone to bias / selective dropout
   - Reduced power
   - Discouraged!

2. **Replace all missing outcomes with a fixed value**
   - eg LOCF, mean, m=s
   - Often used
   - Intuitive appeal
   - Assumed conservative

3. **Replace missing outcomes with predicted value based on modeling**
   - eg. regression imputation
   - Sounds complicated
   - Feasible with standard statistics software
   - More valid than 2.?
Study 1: Alcohol internet intervention (Cohort study)

Original Paper

Missing Data Approaches in eHealth Research: Simulation Study and a Tutorial for Nonmathematically Inclined Researchers

Matthijs Blankers\textsuperscript{1,2}, MSc; Maarten W J Koeter\textsuperscript{2}, PhD; Gerard M Schippers\textsuperscript{1,2}, PhD

\textsuperscript{1}Arkin Academy, Amsterdam, The Netherlands
\textsuperscript{2}Amsterdam Institute for Addiction Research (AIAR), Academic Medical Center, University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands
Problem

How to handle attrition?

Approaches to trial participant attrition compared in simulation study

Heuristic imputation methods
- complete case analysis
- mean imputation
- last observation carried forward

“Simple heuristics”

Model-based methods
- expectation maximization
- regression imputation
- single or multiple imputation (MI)

“using all available data for educated guess”

Which method performs best?
Methods

- Data from prospective cohort study (pre-post design)

  Internet self-help for problem drinkers
  - n=124 had no missing outcome data (Reference)

  Missingness self-induced
  - Missingness at random (MAR) 50% imposed on 1 variable (drinks per day based on TLFB)
  - Missing data approach applied
  - Data analysed
  - Mean drinks per day at follow-up reported

- 75 bootstrapped replications to estimate reliability of the approaches
Results: bootstrapped means

“heuristic approaches”

“model-based approaches”
Conclusions

1. Model-based (multiple) imputation outperformed heuristic approaches
2. Single imputation approaches: EM best
3. MI approaches: Amelia-2 best
4. The approach chosen does matter a lot!
   - Sensitivity analyses needed
Study 2:
Tobacco internet interventions

Original investigation

The Missing=Smoking Assumption: A Fallacy in Internet-Based Smoking Cessation Trials?

Matthijs Blankers PhD\textsuperscript{1,2,3}, Eline Suzanne Smit PhD\textsuperscript{4,5}, Peggy van der Pol PhD\textsuperscript{6}, Hein de Vries PhD\textsuperscript{5}, Ciska Hoving PhD\textsuperscript{5}, Margriet van Laar PhD\textsuperscript{1,6}
Problem

• How to handle differential attrition?

• Missing follow-up smoking status data common in internet-based smoking cessation trials

• Civljak (2013) Cochrane review: ~50% attrition at 6-month follow-up
  • Often differential attrition: 22% differential missingness

• Most common approach to attrition: “missing=smoking”
  • See eg Russell Standard
  • Major journals incl. Cochrane reviews
Study questions

A. Does missing=smoking lead to **conservative** effect estimates compared to complete case analysis?

B. Does model-based imputation lead to **more valid** effect estimates than missing=smoking (under differential attrition)?
Methods (A)

A. Missing=smoking more conservative than complete case analysis?

1. Obtained summary data 22 trials included in Civljak (2013) Cochrane review
2. Extracted from publications numbers smoking / non-smoking and missing at 6 month follow-up
   - Experimental trial arm
   - Control trial arm
3. Calculated effect (RR) estimates using completed cases only
4. Calculated effect estimates assuming all missing to be smoking
5. Compared RR estimates
Results (A)
Results (A)

A. Missing=smoking more conservative than complete case analysis?

- Overall, effect estimates under complete case analysis and missing=smoking were nearly identical
  - Missing=smoking RR: 1.15 [1.00, 1.33]
  - Complete cases RR: 1.14 [0.98, 1.32]

- Missing=smoking results were dependent on trial arm with largest attrition proportion
  - Differential attrition does occur
  - If attrition % was larger in control arm: effects
  - If attrition % was larger in experimental arm: effects
Methods (B)

B. Model-based imputation more valid than missing=smoking?

1. Patient-level data from one RCT (Smit, 2012) in review Civljak (2013) reanalyzed
2. Reference set: all cases with valid smoking status data (n=244)
3. Attrition simulated
   • based on time and trial arm
4. Attrition addressed/imputed using:
   • Missing=smoking
   • Model-based multiple imputation (MICE, van Buuren, 2001)
5. Compared the results to the Reference set
B. Model-based imputation more valid than missing=smoking (under differential attrition)?

1. Plots show deviation from Reference
   - Ideal approach leads to estimates of 0.0

2. Model-based imputation (MICE MI)
   - smaller deviation from Reference

3. Missing=smoking deviation beyond 95% CI (error margins in plot)

4. M=S deviations larger under larger (differential) attrition %.

### Results (B)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline % attrition</th>
<th>6 Weeks % attrition</th>
<th>6 Months % attrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20%</td>
<td>46%</td>
<td>72%</td>
</tr>
<tr>
<td>Experimental</td>
<td>11%</td>
<td>25%</td>
<td>39%</td>
</tr>
</tbody>
</table>
Conclusion

A. Does missing=smoking lead to **conservative** effect estimates compared to complete cases?
- **No**
  - Not when compared to complete cases analysis
  - Not when compared to model-based imputation

B. Does model-based imputation lead to **more valid** effect estimates than missing=smoking (under differential attrition)?
- **Yes**
  - Model-based (multiple) imputation outperforms m=s compared to Reference data
  - This is the case for a variety of attrition scenarios (Blankers et al 2015)
Discussion
Discussion

1. How to handle trial participant attrition?
2. What to do about differential attrition?

- Prevent, prevent, prevent!
- Use model-based (MI) imputation approach
  – Available in SPSS/SAS/Stata/R/…
  – Not difficult to use!

- Assess sensitivity of results to chosen approach
- Refrain from using LOCF and missing=smoking!
Thank you.

Dr. Matthijs Blankers  
(Sr.) Researcher

mblankers@trimbos.nl / matthijs.blankers@arkin.nl

Arkin Mental Health Care, Amsterdam  
Trimbos-institute, Netherlands Institute of Mental Health and Addiction, Utrecht  
Academic Medical Centre, University of Amsterdam  
The Netherlands

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Multiple imputation

Dataset with missing values

Set 1

Set 2

Set k

Results 1

Results 2

Results k

Create new values to replace missing values in dataset

Analyze each new dataset separately

Combined results