

Should individuals with missing outcomes be included in the analysis of a randomised trial?

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Aim

- Consider a randomised trial with missing outcomes.
- 2 principles:

Intention-to-treat (ITT) principle:

- *include everyone randomised*
- *in the group to which they were assigned (whether or not they completed the intervention given to the group)*

Statistical thinking:

- *analysis should be valid under plausible assumptions.*

I will

- show these principles can conflict
- suggest a resolution, which requires all individuals to be included in sensitivity analyses

Plan

1. Background: ITT and missing outcome data
2. Including all randomised individuals in the analysis can be worse than not including them
3. Including all randomised individuals in the analysis can make no difference
4. Proposal for an “ITT analysis strategy”
5. Examples
 - peer review trial
 - smoking cessation trial

1. What does intention-to-treat mean when some outcome data are missing?

- A strict view is that ITT requires complete outcome data
- But researchers with incomplete outcome data also need a principle to guide them
- The revised CONSORT statement is unclear:
 - Abstract: “[Reporting] the number of participants, according to each intervention group, included in the primary data analysis ... allows the reader to judge whether the authors have performed an ITT analysis” (Moher et al, 2001)
 - Explanatory paper: “Although those participants [who drop out] cannot be included in the analysis, it is customary still to refer to analysis of all available participants as an ITT analysis” (Altman et al, 2001)

Note

- We address the **ITT hypothesis**
 - “There is no difference in outcome between these two randomised groups”
 - not the **causal hypothesis** that “The treatments allocated have the same causal effect on outcome”

2. Including all randomised individuals in the analysis can be **worse than** not including them

Some questionable methods include all randomised individuals

- Missing = failure
 - may be a reasonable starting point e.g. in smoking cessation trials
 - but we don't believe that success \Rightarrow observed
- Last observation carried forward (LOCF)
 - OK if you really believe its implicit assumptions (but we rarely do)
 - often claimed to be conservative (but often conservatism for the group mean is confused with conservatism for treatment effect)
 - widely critiqued e.g. Mallinckrodt et al (2004)

EMA (European drugs regulator)

- Points to consider on missing data, 2001:
 - “The statistical analysis of a clinical trial generally requires the imputation of values to those data that have not been recorded ...”
 - “Last observation carried forward ... is likely to be acceptable if measurements are expected to be relatively constant over time.”
- Draft revision, 2009:
 - “single imputation methods, including LOCF ..., can be accepted as a primary analysis in confirmatory trials provided that the applicant has justified that the estimated treatment effect is not expected to be biased in favour of experimental treatment”

Some reasonable methods don't include all randomised individuals

In a single-measure trial, complete cases analysis may be reasonable

- includes all individuals with observed outcome
- adjust for baseline variables
- analysis is valid under missing at random (MAR)

In a repeated-measures trial, a mixed model analysis may be reasonable

- includes any individual with ≥ 1 outcome observed
- excludes those with no outcomes
- also valid under MAR

MAR is often more plausible than other assumptions

3. Including all randomised individuals in the analysis can be **the same as** not including them

Multiple imputation

- Impute missing (single or longitudinal) outcomes from observed outcomes and baselines
- Then analyse the completed data
- Example with single outcome (Web-based self-help for problem drinkers: a pragmatic randomized trial. Riper et al, *Addiction* 2008):
 - “We then performed intention-to-treat analysis, using multiple imputation to deal with loss to follow-up.”
- We know this is the same as fitting a (mixed) model to the observed data if
 - imputation model and analysis model are the same
 - large number of imputed data sets

Joint modelling of baseline and outcome

This mixed model includes all individuals in the analysis:

- baseline:
- follow-up:

$$\begin{array}{l} y_{i0} = \alpha_0 + e_{i0} \\ y_{i1} = \alpha_1 + \beta R_i + e_{i1} \end{array}$$

outcomes randomised group

- e_{i0} , e_{i1} are correlated
- Note no treatment effect at baseline
- No missing y_{i0} \rightarrow estimate of β is the same as from ANCOVA

Example: UK700 trial

- Intensive vs. Standard case management for severely mentally ill people living in the community
- 708 patients randomised in 4 UK centres
- Outcome here: CPRS (psychopathology) score from 2-year interview
 - missing in 11% of Intensive arm, 20% of Standard arm.

Method	Patients in analysis	Treatment effect	Standard error
ANCOVA	595	-0.3898	1.0348
Joint model	705	-0.3898	1.0304
Multiple imputation	708	-0.3834	1.0369

Monte Carlo error 0.0135

Summary so far

- Including all randomised individuals in the analysis isn't enough
- The desire to include all randomised individuals in the analysis
 - has led to a preference for a dubious method (LOCF) over a less dubious method (mixed models)
 - reduces emphasis on the appropriate assumptions
 - may lead to use of unnecessarily complex methods
- How else can we define ITT?

4. Proposal for an ITT analysis strategy

1. Is based on an ITT **design** that aims to collect all outcome data on all randomised individuals
2. Includes a main analysis that
 - Keeps individuals in their randomised groups
 - Analyses all available outcome data
 - Is valid under a named **plausible assumption** about the missing data
3. Includes **sensitivity analyses** that consider a range of plausible alternative assumptions about the missing data
 - the alternative assumptions should contradict the main assumption
4. **All individuals should be included in the sensitivity analyses**

5. Examples: Peer review trial

- Peer reviewers were randomised to postal training or control (we ignore a 3rd arm)
- Outcome: quality score of a subsequent review

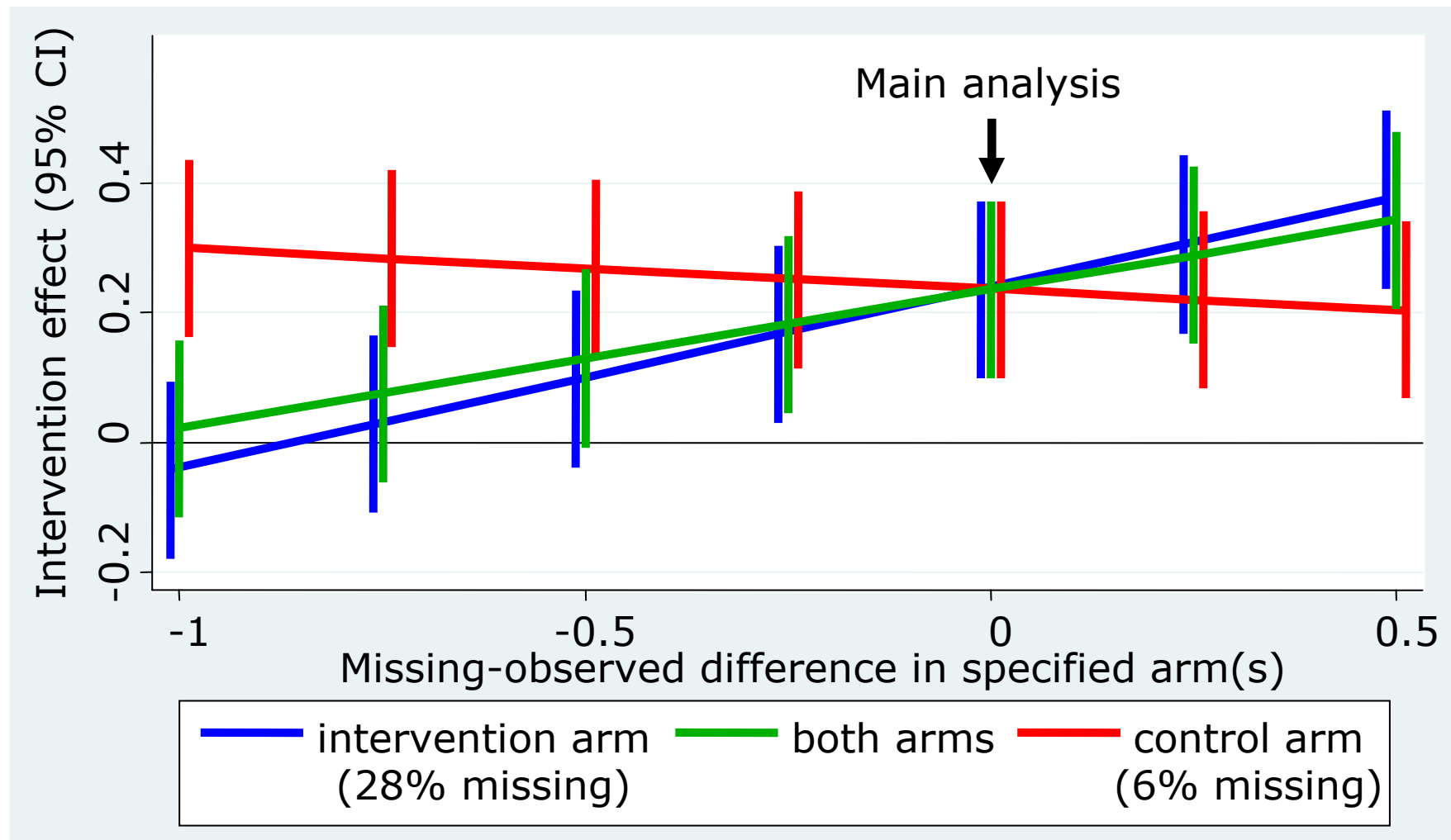
	Control	Postal training
Total n	173	166
Missing outcome	6%	28%
Mean of observed outcomes	2.56	2.85
SD of observed outcomes	0.64	0.64

Postal vs. control, baseline adjusted:
difference = 0.24 (se 0.07)

Peer review trial: analyses

- **Main assumption:** no difference between missing and observed values, once adjusted for baseline variables (MAR)
- **Main analysis:** analysis of covariance on complete cases
- **Sensitivity analysis:** consider possible differences between missing and observed values, allowed to be different in each arm

Peer review trial: sensitivity analysis



Example 2: smoking cessation trial

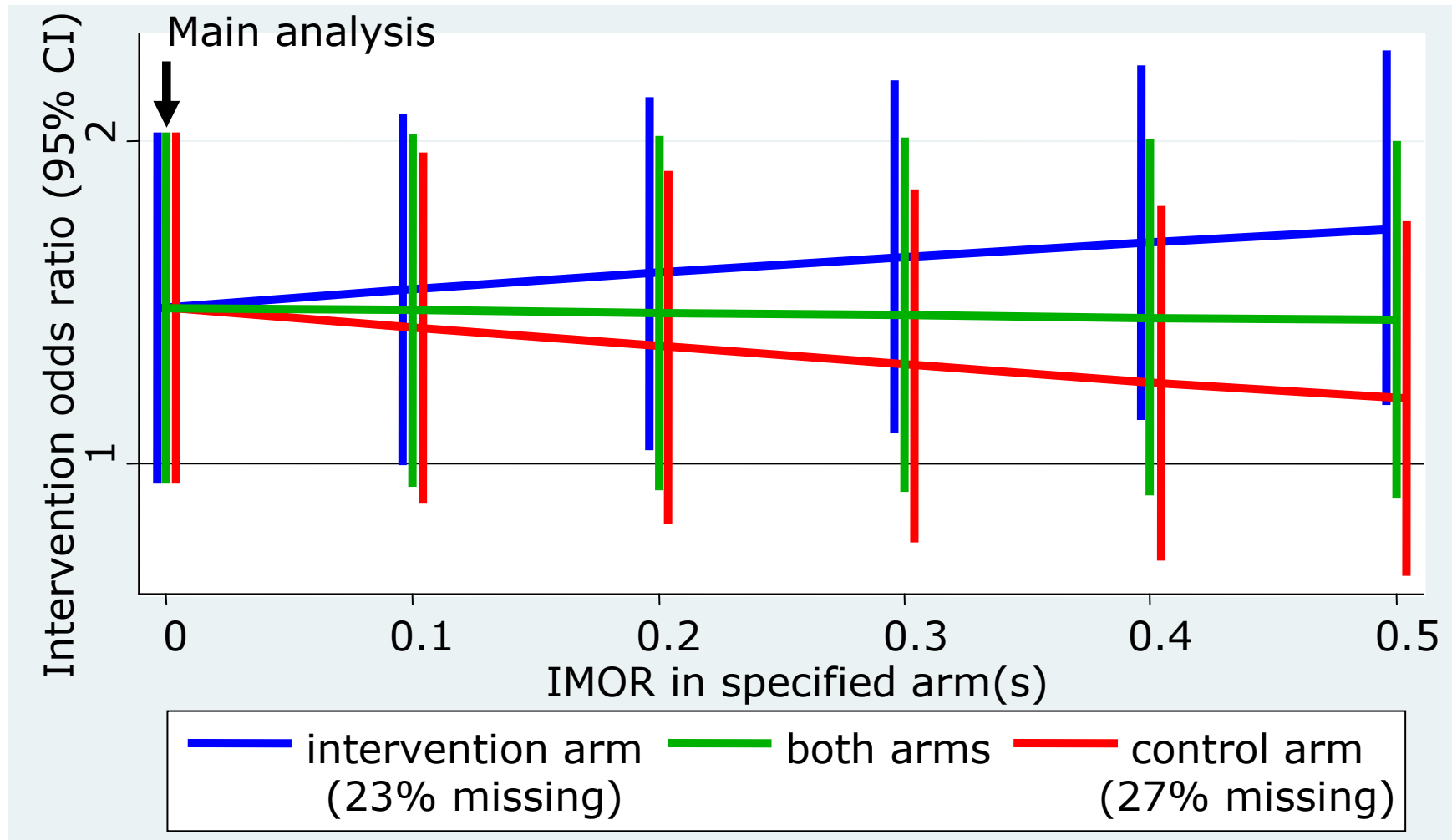
- Smokers calling a telephone helpline were randomised to tailored advice letters + standard counselling or standard counselling
- Outcome: not smoking in months 4-6 ("quit")

	Intervention arm (n=599)	Control arm (n=565)
Quit	73 (12%)	51 (9%)
Didn't quit	390 (65%)	364 (64%)
Missing	136 (23%)	150 (27%)

Smoking cessation trial: analyses

- **Main assumption:** assume missing = still smoking (Sutton & Gilbert, 2007)
 - Includes everyone, but not convincing
- **Main analysis:** impute missing values as smokers
- **Sensitivity analyses:** define the informatively missing odds ratio (**IMOR**) as the odds ratio between quitting and missing
 - main analysis assumes $IMOR=0$
 - sensitivity analysis varies IMOR (in one or both arms)

Smoking trial: sensitivity analysis



Summary: ITT analysis strategy

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 - the alternative assumptions should contradict the main assumption
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The end

References

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Summary

- Intention-to-treat should be implemented as an **analysis strategy**
- Inclusion of all randomised individuals is not a useful criterion for a main analysis
 - but inclusion of all data is
- All individuals must appear in sensitivity analyses

Molenberghs et al (Biostatistics 2004)

- “A likelihood based ignorable analysis should be seen as a proper way to accommodate information on a patient with postrandomization outcomes, even when such a patient’s profile is incomplete.
- “This fact, in conjunction with the use of treatment allocation as randomized rather than as received, shows that [a mixed model analysis] is fully consistent with ITT.”