ADVANCES IN THE TREATMENT OF MISSING DATA

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1. SOME OPENING POINTS

- Assessment of the validity of a statistical analysis cannot be separated from the goal of the analysis.
- The validity of the conclusions drawn from any statistical analysis depends on assumptions.
- Missing data: data we intended to collect but could not.

  What is missing *may depend on the goal of the analysis.*
- The occurrence of missing data introduces ambiguity into any conclusions drawn from a statistical analysis, that can only be resolved with additional assumptions that cannot themselves be assessed from the data under analysis.
- Question: should the occurrence of missing data change the goal of the analysis?

In what follows I will focus on dropout/withdrawal/loss-to-follow-up/attrition.

To me, these points lead to (among other things) a vital distinction:

- Is dropout defined to be part of the *outcome*, or a *nuisance* to be accommodated, (*i.e.* one that prevents us measuring what we want to measure)?
- The former is very common when various form of simple *imputation* are used, with Last Observation Analysed perhaps the best known example.
- Such a procedure *defines away the missing data*, *i.e. there are no missing data.*
- In principle the subsequent analysis will be valid (other aspects being appropriate), but what is the *clinical meaning* of the subsequent conclusions?
- Such an approach runs the risk of making the classic analysis error: when in doubt, provide a valid answer to the wrong question.
- In the following I focus on *dropout as a nuisance*.

(2) CONCEPTS, ISSUES, DEFINITIONS

From the US NAS Report we have the concept of the *estimand*: I will use this to encapsulate the goal of the analysis.

We want to estimate and/or test hypotheses about this quantity.

Define two types of estimand

[The following is based on:

Analysis of longitudinal trials with missing data: a framework for relevant, accessible assumptions, and inference via multiple imputation

by Carpenter, Roger, Kenward.]

de jure

Estimate the treatment effect under the best case scenario.

Does the treatment work under the best case scenario?

[Per-Protocol, PP, efficacy]

de facto

Estimate the effect seen in practice if this treatment were applied to the population defined by the trial inclusion criteria.

Is an effect seen in practice if this treatment is applied to the population defined by the trial inclusion criteria?

[Intention To Treat, ITT, effectiveness]

How are missing data then defined as missing?

This depends on the estimand, and for this we need to introduce

the deviation from the protocol relevant to the estimand

[or *deviation* for short]

Following deviation subject's data are set to missing.

e.g. for *de facto* questions we *typically* regard the first instance of the following as deviations:

- unblinding, for example of treatment allocation, and
- loss to follow-up (after which no data are available in any case);

whereas the following would typically not be deviations:

- moving to partial compliance with treatment, and
- withdrawal from treatment (e.g. following an adverse event).

and for *de jure* questions, we *typically* regard the first instance of any of these as deviations:

- unblinding;
- moving to partial compliance with treatment;
- withdrawal from treatment, and
- loss to follow-up.

(3) MISSING DATA MECHANISMS AND THE ROLE OF MAR.

From a frequentist perspective, for dropout (deviation):

Definition: Missing Completely at Random (MCAR)

- The probability of a subject dropping out (deviating) is independent of outcomes, seen or unseen, or any other variables in the analysis.
- Any analysis valid for the whole dataset is valid for the observed data.

Definition: Missing at Random (MAR)

- The probability of a subject dropping out is conditionally independent of future (current) observations, given the observed history.
- Under MAR, likelihood based analyses of the outcome only are valid (the actual dropout mechanism can be ignored).
- Non-likelihood methods (*e.g.* such as GEE/moment based) will need to use the dropout mechanism explicitly to be valid.

Another view of MAR:

The future statistical behaviour of the observations from a subject, conditional on the history, is the same whether the subject drops out (deviates) or not in the future.

Implications:

- The future behaviour of dropouts can be modelled using future behaviour of those who remain.

  This implies that treatment behaviour can be borrowed.

- Analyses that capture this behaviour properly, i.e. likelihood based, will be valid, when others such as GEE/moment based, may not be.
- A key issue in the longitudinal setting is correctly representing the regression of the future on the past.

Definition: Missing Not at Random (MNAR)

- The probability of a subject dropping out is conditionally *dependent* on future (current) observations, given the observed history.
- Equivalently:

  The future statistical behaviour of subjects is not the same for those who drop out and those who don't, even if the their history is identical.
- Valid analyses need to take account of the missing value mechanism, which is usually not known.
- This can be done *indirectly.*

The role of MAR.

- There has been a lot written about methods of analysis that are valid under MAR.
- We know that with likelihood based methods (broadly) the dropout mechanism is ignorable.
- There are non-likelihood methods that use inverse probability weighting.
- The two can be combined (in a certain sense) using doubly robust methods.

[For example:

Molenberghs G and Kenward MG (2007) *Missing Data in Clinical Studies.* Chichester: Wiley.

Tsiatis A (2006) *Semiparametric Theory and Missing Data.* New York: Springer.]

We can use comparatively simple likelihood based analyses under MAR, *e.g.* for a continuous outcome:

the multivariate normal linear model with unstructured covariance matrix and full time-by-treatment interaction.

Sometimes called a Mixed Model Repeated Measurements (MMRM) analysis (unfortunately in my view).

[Molenberghs G and Kenward MG (2007) *Missing Data in Clinical Studies.* Chichester: Wiley.]

- What about other outcomes? *e.g.* binary.
- Likelihood can be awkward for **marginal/population averaged** models, **Generalized Estimating Equations** (GEE's) are commonly used instead.
- These are not valid in general under MAR.
- Alternatives:
  - Use subject specific models for which likelihood analyses are the norm.

    But this changes the interpretation of the parameters.

    Scale the parameters appropriately?
  - Use **Multiple Imputation** with a sufficiently rich and tractable (*e.g.* loglinear) imputation model which is uncongenial.
  - Use **inverse probability weighted estimating equations** with a marginal model, and doubly robust extensions.

How does MAR fit in with the *de jure* and *de facto* questions?

Recall, MAR dropout implies

the future statistical behaviour of a subject, conditional on the history, is the same whether the subject drops out or not in the future.

That is, both outcome and *future treatment use*, follow the same conditional distributions for all subjects.

- This would lead to the testing of a *de jure* hypothesis if treatment compliance before dropout matches the protocol.
- Or, extending this, if there were withdrawal, all post-withdrawal outcomes were set to missing.
- Or, if future treatment compliance after dropout matched that expected in use in the population, this would lead to the testing of a *de facto* hypothesis.

(4) DEPARTURES FROM MAR AND SENSITIVITY ANALYSIS

Recall from earlier: how does MAR fit in with the *de jure* and *de facto* questions?

Broadly, MAR dropout implies

the future statistical behaviour of a subject, conditional on the history, is the same whether the subject drops out (deviates) or not in the future.

That is, both outcome and *future treatment use*, follow the same conditional distributions for all subjects.

- This would lead to the testing of a *de jure* hypothesis if treatment compliance before dropout matches the protocol.
- Or, extending this, if there were a deviation, all post-deviation outcomes were set to missing.
- Or, if future treatment compliance after dropout matched that expected in use in the population, this would lead to the testing of a *de facto* hypothesis.

- But this excludes many common settings.
- So, often it is likely that we need to consider NMAR models.
- How should this be done?
- A secondary analyses? As part of a sensitivity analysis?

Very broadly we can distinguish two important ways of approaching departures from MAR in settings like this.

- **Route 1:** Consider an explicit MNAR dropout (deviation) mechanisms.

  i.e. modify

  $$\mathrm{P}(R \mid \mathbf{Y}_O, \mathbf{Y}_M)$$

  This is naturally approached using *selection models*.

- **Route 2:** modify directly the future behaviour of dropouts (those who deviate), *i.e.* modify

  $$f(\mathbf{Y}_M \mid \mathbf{Y}_O, R)$$

  This is naturally approached using *pattern-mixture models*.

- In fact there is a third route: so-called **shared-parameter models**
- These have latent variables that are linked to both outcomes and dropout indicators.
- They fit very naturally within the **Structural Equation** framework – and have received a lot of attention in the social science setting.
- To me, it is not obvious from these exactly what form is being implied either for the future behaviour of dropouts or for the selection process.
- Perhaps useful for some sensitivity analyses?
- A recent example in a clinical trial setting: Kenward and Rosenkranz (2011) *Journal of Biopharmaceutical Statistics*, **21**, 252-262.

There are many ways of approaching sensitivity analyses:

- Sensitivity parameters
- Pattern-mixture/selection models
- Likelihood based/full enumeration regions
- Multiple imputation based
- Incorporating prior belief (Bayes)

The generic sensitivity problem in the dropout (deviation) setting

1. Define the specific questions, and consequent quantities to be estimates, and hypotheses, that we wish to test;
2. define the nomenclature for departures from protocol;
3. frame the relevant accessible assumptions, and
4. formulate the procedures for estimation and inference.

By contrast, a shopping list of alternative analyses with no obvious relation to the estimand of interest, or to the assumptions underlying the primary analysis, does not, in my opinion, constitute a sensitivity analysis.

Being arbitrary (even in consistent way) is not an acceptable response to ignorance.

(5) SUMMING UP

(1) Analysis of trials with partially observed data (deviations) requires making untestable assumptions. Therefore:

- design to minimise missing data (deviations);
- collect off-treatment data where possible;
- pre-specify key assumptions for patients who withdraw for various reasons;

(2) Apply standard statistical principles:

- make assumptions;
- obtain valid inference under the assumptions
- check the robustness of the conclusions as the assumptions change
- Talking about a conservatively biased estimator doesn't make sense without first specifying the assumptions about the missing data (deviations).

(3) Specifying LOCF and then debating whether it is conservative or not in a particular leads to unilluminating discussion.

Methods

1. Think carefully about the question the analysis is addressing.
2. Sensitivity analysis is key, and needs to be accessible and relevant:
   - I would argue that formulating the assumptions through the pattern mixture approach (re James Roger's talk later) is accessible to most collaborators;
   - the more accessible the assumptions, the more likely the analyses are to be relevant;
   - given the assumptions, valid estimation is straightforward via multiple imputation.

References

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