

Incomplete and Enriched Data Analysis and Sensitivity Analysis presented by Geert Molenberghs

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Statistics SIAC, VJC, January 13, 2010

Withdrawals in longitudinal studies

Intermediate observations are taken of the response (and possibly other outcomes) at intermediate visits up until withdrawal or completion.

I suggest that this is not primarily a *missing data* problem

- ▶ If subject withdraws as a result of death then there is no 'missed' observation.
- ▶ It may not be safe for the subject to continue treatment.
- ▶ Withdrawal in some cases is imposed by the protocol, rather than a choice of the patient/physician.
- ▶ There are any reasons for withdrawal. Can one approach fix all?

Discussion from Geert's paper at the DIA meeting in 2009

Paul Flyer (DIJ, 43, 437-439)

- ▶ *It appears at the present time that there is great enthusiasm for the discussion of the relative merits of various missing data strategies without sufficient thought to what we are trying to demonstrate in a clinical trial.*

When subjects have missing data clearly related to treatment (AEs, lack of efficacy, protocol deviations, etc) the use of observed data for estimation is based on a desire to predict what would have happened had the subject stayed on treatment.

Unfortunately one cannot use a randomized trial to provide an interpretable estimate of what would have happened if subject were able to remain on treatment.

MAR analyses

- ▶ Current MAR analyses answer the question "what if everyone had received treatment up to the final visit.
- ▶ Most MNAR analyses aspire to the same end but attempt to allow for uncontrollable selection bias.
- ▶ What if we want to estimate the effect of treatments under more realistic post-withdrawal scenarios?
- ▶ Assume post withdrawal that patients move to some common regimen and then estimate margin at final time.

Pattern mixture in an Multiple Imputation (MI) framework

- ▶ Multivariate normal distribution.
- ▶ MI under MAR assumption imputes assuming the pattern of means is same after withdrawal as before.
- ▶ Alternative is to impute borrowing the pattern post-withdrawal from other arms such as a positive control arm.
- ▶ ...or perhaps from shared shared post withdrawal data.

Same idea in a direct likelihood approach

- ▶ Possible to embed the same idea into a direct likelihood approach, with some very minor differences.

Conclusion

- ▶ Rather than 'Sensitivity analyses' that focus on the impact of alternative withdrawal mechanisms . . .
... try to estimate impact of treatment at final visit.
- ▶ Multiple imputation with pattern mixture model is a possible way to do this.