Missing Data in Outcome Trials: Implications and Prevention

Cardiac Safety Research Consortium

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Recent Reports

- National Research Council (2010). *The Prevention and Treatment of Missing Data in Clinical Trials*. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, The National Academies Press.

- Little RJ et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012;367:1355-1360.

- Little RJ et al. The design and conduct of clinical trials to limit missing data. *Stat Med* 2012; 31:3433-3443.

Panel Report

- 18 recommendations
  - 8 on prevention through design and conduct
  - 7 on methods, including sensitivity analysis
  - 3 on data sharing, training and future research

Key Points

- **Treatment discontinuation ≠ withdrawal of consent.**
- **Withdrawal of consent may ≠ discontinuation of all data collection.**
- **Missing data can be prevented by:**
  - Trial design
  - Trial conduct, including appropriate choice of sites/investigators

"Analysis" and "Treatment" Dropouts Are Not the Same

- While "analysis" dropout usually implies "treatment" dropout, reasons for these types of dropout vary

- Reasons for "analysis" dropouts:
  - Withdrawal of consent by patient or legally authorized representative
  - Patient moves away or cannot be contacted

There are Many Misconceptions About Withdrawal of Consent

- It is not the investigator's decision; it is the patient's (at least, these should be differentiated)
- Treatment discontinuation ≠ withdrawal of consent
- Unwillingness to attend follow-up visits ≠ withdrawal of consent

Withdrawal of Consent

A key element of the consent form:

45 CFR 46.116 (b)(4):

“The consequences of a subject’s decision to withdraw from the research and orderly termination of participation by the subject”

FDA Guidance on Data Retention When Subjects Withdraw from FDA-Regulated Trials

- When a subject withdraws, data collected up to time of withdrawal cannot be removed from database
- Investigator may ask subject if they wish to provide additional data collection following discontinuation of intervention
- Additional data collection following discontinuation of intervention requires consent
- Following withdrawal, medical and other confidential records cannot be used but public records (e.g., survival status) may be used

Good Clinical Practice Program and Office of Chief Counsel, October 2008.

Withdrawal Language for Consent

If you or your doctor decide it is best not to take the study drugs, other treatment options will be discussed with you. You will continue to be scheduled for follow-up visits every 4 months until the study ends. Your continued participation is very important in order to reliably answer the study question.

Important Predictors of Missing Data Are Not Patient Related

- Research has usually focused on patient characteristics:
  - Younger age
  - Smokers
  - Socioeconomic status – employment, stable housing, education
- Helpful to a degree, but these are not the major risk factors

More Important Factors

- Clinical research site (whether source of primary care, stability, experience, number of patients enrolled, staff turnover)
- Trial design (write protocols with easily ascertainable outcomes and follow all randomized participants until the end of the trial).
- Trial conduct conditions
- Quality assurance procedures

Etiology of Missing Data

Trial protocol

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Selection and training of investigators

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Informed consent

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Trial conduct conditions

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Monitoring against realistic, but high, performance goals

Etiology Suggests the Following for Primary Prevention

- Write protocol with minimization of losses in mind (do not overburden patients and staff).
  - Avoid complicated and cumbersome record keeping.
  - Make it easy to obtain prescriptions.
  - Choose easily ascertainable endpoints.
- Select sites in a convenient location for patients with demonstrated record of excellent follow-up.
- Train study staff (and sponsors) on the importance of excellent follow-up (minimizing missing data).
- Fully inform patients of trial requirements and importance of full participation during consent process.

Panel Report: Actions for Design and Data Management Teams

- Select clinical sites/investigators with good track record
- Provide continued access to effective treatments after the trial, before treatment approval
- Create a “no missing data” mindset in your organization
- Monitor data collection against pre-specified targets

A Perspective from 35 Years Ago

- “Rigorous entry criteria are not necessary for a randomised trial, but rigorous follow-up is.”
- “One excellent policy is to accept no withdrawals under any circumstances.”
- “Patients who move away from the centres where they were admitted to the trial should not be allowed to disappear from the trial.”
- “…our policy is to accept no reason for loss except emigration…”

Peto R, Pike MC, Armitage P, et al. Br J Cancer 1976.

Summary

- **Missing data undermine the credibility of trial conclusions.**
- **It is possible to do trials with little missing data.**
- **Be prevention minded.**
- **Set higher standards.**