Minimizing Missing Data in the Design of Observational Clinical Studies: A Regulatory Perspective

Lilly Q. Yue*

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993

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Abstract

Substantial amount of missing data is not uncommon in medical product clinical studies, particularly for medical devices, and this creates great challenges in the interpretation of study results. Compared to randomized clinical trials, observational studies may present even more hurdles. To reduce the frequency and minimize the impact of missing data, sufficient attention has to be paid at the study design stage. In this talk, some design issues related to missing data will be discussed and illustrated through examples from medical device pre-market regulatory submissions.

1. Introduction

Pre-market observational studies could be concurrent comparative studies, partial concurrent/non-concurrent comparative studies (e.g., with historical control) or single arm studies. Post-market studies are usually observational in nature, e.g., registry studies. Observational studies share all missing data problems with randomized controlled clinical trials, and in addition, may have more issues coming from the following limitations and challenges. In observational studies, blinding may not be physically possible for the patient, primary physician or sometimes even a third-party evaluator; unlike the presence of a drug in a pill, the presence or use of a medical device may be obvious; the implantation of a medical device may have failed; an implanted device may need to be removed; cross-over or rescue treatment may be necessary; patient compliance could be much poorer. All of these could lead to substantial amount of missing data in both treatment groups, and different missing pattern across the treatment groups, which could jeopardize the validity of study design and interpretation of study results. Therefore, it is even more crucial to make great efforts in prevention and treatment of missing data in such studies.

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Data in clinical studies could be missing by study design or by study conduct. Missing data could occur in clinical outcomes or baseline covariates. This presentation is intended to promote efforts that need to be made at the design stage to reduce the frequency and impact of missing data, rather than to provide specific suggestions on how to reduce missing data in any particular study. Along with examples, the issues discussed in this paper include minimize missing data in clinical outcome determination and assessment, in covariate collection and in national registry. Also, some regulatory issues will be briefly discussed followed by a summary that concludes the best treatment of missing data is to minimize or eliminate missing data in study design and conduct.

2. Minimize Missing Data in Study Design

The National Academy of Science (NAS) Committee on National Statistics made the following recommendations (National Academy of Sciences, 2010).

Recommendation 2: Investigators, sponsors, and regulators should design clinical trials consistent with the goal of maximizing the number of participants who are maintained on the protocol-specified intervention until outcome data are collected.

Recommendation 6: Study sponsors should explicitly anticipate potential problems of missing data. In particular, the trial protocol should contain a section that addresses missing data issues, including the anticipated amount of missing data, and steps taken in trial design and trial conduct to monitor and limit the impact of missing data.

2.1 Minimize missing data in outcome determination and assessment.

Clinical outcomes should be appropriately defined so that the assessments of outcomes could be achieved from a high portion of patients.

Example 1. A cardiovascular device was compared to an optimal medical therapy. One of clinical outcomes was the change from baseline in 6-minute walk distance on treadmill. A substantial amount of missing data occurred due to the fact that some patients were too sick to complete the 6-minute walk or too nervous to walk, some missed the visits and some dies. An immediate question would be how to reduce missing data in this case? And, are there other more appropriate clinical outcomes with less missing values?

2.2 Minimize missing data in Baseline covariate collection

In comparative observational studies, two treatment groups could be quite different in patient population, definition and adjudication of clinical outcomes, collection of important baseline confounding covariates and timing and length of follow-up. The heterogeneity between the treatment groups could compromise the validity of study results. Fortunately, some existing sophisticated statistical methods could be utilized for possible remedies, e.g. propensity score methodology. Propensity score is conditional probability of receiving treatment A rather than treatment B, given a collection of observed covariates. The propensity score methodology could be used to approximate RCT by simultaneously balancing the observed baseline covariates, and then reduce bias in treatment comparison with respect to outcomes. A key assumption underneath is

ignorability, i.e. there are no unobserved treatment differences between the two treatment groups, conditional on the observed covariates. To satisfy the assumption, all covariates known to be related to both treatment assignment and/or outcomes should be collected in the study and included in propensity score modeling, as excluding a key covariate could lead to substantially biased treatment effect estimation. On the other hand, without any action on the missing covariate values, patients with at least one covariate value missing would be excluded from propensity score modeling of logistic regression and then from treatment comparison with respect to clinical outcomes. Consequently, extensive missing data on key covariates could comprise the reliability of study results.

Example 2. A Pediatric cardiovascular device was evaluated through comparison to a control group selected from an existing registry. Propensity score matching was used to form a control group and make treatment group comparison. Body surface area (BSA) was known to be an important variable affecting the primary effectiveness endpoint. However, it was collected only in the current investigational study, but missing in the registry group. Consequently, the missing data complication added great difficulty in the interpretation of treatment comparison results and regulatory decision making.

2.3 Minimize Missing Data in National Registry

Some national medical device registries have been established for post-market surveillance of safety and effectiveness, post-approval studies, quality improvement, observational research, and public source of information. The registries may also be utilized for pre-market evaluation purpose such as expanding indication for use (there might be some ethical issues, e.g., informed consent requirement), labeling change or forming a control group for a new investigational study.

For a registry database to serve the purposes as intended, the registry data should be of high quality, comprehensive, complete and reliable. All relevant information, including all key baseline covariates and clinical outcomes, needs to be collected. There should be no excessive number of subjects who withdrew from the study or were lost to follow-up. The missing data should be minimized. There are some good examples of national registry, e.g., the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and Transcatheter Valve Therapy (TVT) Registry.

INTERMACS is a collaborative effort made by academia, industry and government agencies, including NIH, CMS, FDA, the university of Alabama Birmingham and industry sponsors. The primary purpose of this registry is to track outcomes of patients who receive approved mechanical circulatory support devices in the US. All parties made great efforts in the pre-planning, involvement, and cooperation to ensure that complete and robust data were to be captured so that the registry data would likely be adequate for device evaluation. The important issues were addressed regarding collection of all important covariates needed for pre- and post-market evaluations and assurance of high quality data via the effective protocols in place. The registry was used to form a control group for the pre-market evaluation of a new investigational device.

The TVT registry was designed to monitor the safety, effectiveness, and real-world outcomes for TVT in US. Developed in 2011, the registry is jointly operated and managed by the Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC), in close collaboration with the FDA and CMS, for post-market data

collection on transcatheter aortic valve replacement (TAVR) procedures. As of July 9, 2014, the registry includes 18,125 patient records from 260 medical centers in US. The information collected in the registry includes

- patient, provider, and facility characteristics
- patient history and risk factors, including cardiac status and detailed health status (e.g., quality of life)
- pre-, intra-, and post-procedure data points and adverse events
- outcomes at 30 days and one year.

Data are entered by designated hospital employees directly into the registry's electronic platform, and then transferred to the ACC's National Cardiovascular Data Registry (NCDR) and verified for completeness, consistency, and accuracy. Data report is generated weekly and missing data on the quality of life measurements are reduced.

2.4. Sample Size Adjustment

In the sample size estimation, a traditional adjustment for missing data is as follows

$$N(adj.) = N/ (1- p), \quad p: \text{anticipated drop-out rate}$$

A misleading perception is that with the sample size adjustment, the negative impact of missing data has been adequately corrected. However, the adjustment is valid only under the assumption of missing completely at random (MCAR), which rarely holds. Also, this adjustment only addresses the variability but not the bias introduced by missing data. In fact, it produces more precise biased estimates for parameters of interest, as pointed out by Fleming (Fleming, 2011). Best approach to addressing missing data is to prevent it.

3. Some Regulatory Issues

The National Academy of Science (NAS) Committee on National Statistics also made the following recommendations:

- **Recommendation 9**: Statistical methods for handling missing data should be specified by clinical trial sponsors in study protocol, and their associated assumptions stated in a way that can be understood by clinicians.

- **Recommendation 15:** Sensitivity analyses should be part of the primary reporting of findings from clinical trials. Examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting.

In study protocol, if possible with any experience, the types and amount of potential missing data should be anticipated, e.g., missing data due to procedure failures. The types of missing data should be classified into categories and then different missing data handling strategies should be pre-specified, e.g., how to classify and handle a patient with missing outcome due to a procedure failure. Appropriate patient populations should be defined for effectiveness and safety evaluations, relative to missing data handling. Furthermore, statistical methods of handling missing data should be pre-specified and sensitivity analyses of study results to deviations from underlying assumptions need to be

planned. In addition, all patients should be accounted for in the reports submitted to the FDA.

4. Conclusion

Minimizing the amount of missing data in outcomes and covariates is of greater importance in observational studies than randomized trials. Great efforts are needed in study design stage to minimize missing data and non-compliance. It is critical to appropriately define clinical outcomes and set proper follow-up schedule to avoid a substantial amount of missing data. A good strategy is needed on the collection of key baseline covariates. The statistical methods of handling missing data and plan for sensitivity analyses should be pre-specified in protocol. ***The best way to handle missing data is to have no missing data!***

References

National Academy of Sciences. (2010). The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials, National Research Council. Washington, DC: National Academies Press.

Fleming, TR. (2011). Addressing Missing Data in Clinical Trials. *Ann Intern Med.* 154 (2):113-117.