

SISCER 2024
Special Topics in Clinical Trials
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Over many decades, the randomized clinical trial has become the gold standard for evaluation of new drugs, biologics, devices, procedures, and behavioral interventions. In these presentations, two topics of central importance will be discussed that have broad implications in the design and conduct of clinical trials: the Design of Non-Inferiority Trials and the Prevention of Missing Data.

Addressing Missingness: Missing data on outcome measures in clinical trials meaningfully reduce the integrity and interpretability of results, adversely affecting science and thus the medical community pursuing an evidence-based practice of medicine. The effect is substantial when a nontrivial fraction of patients has missing data on primary and secondary efficacy and safety end points in the trial and when mechanisms for missingness are related to or informative about the outcome measures. For too long, there has been overreliance on methods to adjust for missing data in clinical trials. Worse yet, these methods often have been naively inadequate, such as making adjustments in sample size that address the variability but not the bias induced by missingness or using simplistic approaches, such as last-observation-carried-forward, complete-case, or worst-case analyses. Although rational imputation methods may be useful to treat missingness after it has occurred, such methods depend on untestable assumptions. The preferred and often only satisfactory approach to addressing missing data is to prevent it. Procedures should be in place to maximize the likelihood that outcome data will be obtained at scheduled times of evaluation for all surviving patients who have not withdrawn consent. To meaningfully reduce missing data, it is important to recognize and address many factors that commonly lead to higher levels of missingness. These issues will be discussed in detail in this presentation. There is wisdom in the recognition that “*an ounce of prevention is worth a pound of cure.*”

Design of Non-Inferiority Trials: Suppose a standard therapy has been established to provide a clinically important reduction in risk of irreversible morbidity or mortality. In that setting, the safety and efficacy of an experimental intervention often would be assessed in a clinical trial providing a comparison with that standard therapy rather than with a placebo arm. Such a trial often is designed to assess whether the efficacy of the experimental intervention is not unacceptably worse than that of standard therapy, and is called a non-inferiority trial. Formally, the non-inferiority trial would be designed to rule out a non-inferiority margin, defined as the minimum threshold for what would constitute an unacceptable loss of efficacy. In this session, we will present scientific insights into many factors that should be addressed in the design and conduct of non-inferiority trials to enhance their integrity and reliability. Among essential considerations are recognizing the importance of the Constancy Assumption, addressing uncertainty about its validity, and properly formulating the non-inferiority margin. We also will provide insights from recent experiences that illustrate the successful design and conduct of non-inferiority trials, and then provide recommendations and conclusions regarding best practices in their use.

OUTLINE

In two 90-minute presentations, we will review Methods for Addressing Missing Data, and the Rationale and Role for Non-inferiority Trial Designs. Current best practices will be described, and examples will be shared of the successful implementation of these methods.

Session 1 (Virtual): July 15, 2024: Addressing Missing Data

- A. Factors contributing to Missing Data
 - B. Approaches to Addressing Missingness
 - C. Inherent Limitations of Approaches for Treating Missing Data
 - D. The Successful Prevention of Missing Data: Illustrations and Conclusions
- Fleming TR. Addressing Missing Data in Clinical Trials. *Annals of Internal Medicine* 154: 113-117, 2011.
 - National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: National Academies Pr; 2010.

Session 2 (Virtual): July 15, 2024: Issues in Non-Inferiority Trials

- A. Motivating the Proper Role of Non-Inferiority Trials
 - B. The Constancy Assumption: Recognizing its Importance and Addressing Uncertainty about its Validity
 - C. Determining the Non-Inferiority Margin
 - D. Illustrating the Successful Design and Conduct of Non-Inferiority Trials
- Fleming TR, Odem-Davis K, Rothmann MD, Shen YL. Some Essential Considerations in the Design and Conduct of Non-Inferiority Trials. *Clinical Trials* 8:432-439, 2011.