

SCT 2012 Pre-Conference Workshops

Workshop Schedule
Sunday, May 20, 2012

Morning (8 a.m. – 12 p.m.)	Afternoon (1 p.m. – 5 p.m.)
1. Essentials of Randomized Clinical Trials	
2. Trial and Site Management for Multi-Center Trials	6. Challenges and Strategies of Clinical Data Management
3. Practical Statistical Reasoning in Clinical Trials for Non-Statisticians	7. CDISC: What are the Standards, How Will They Help, and How to Adapt?
4. Adaptive Clinical Trials	8. Statistical Procedures for Interim Analysis in Clinical Trials
5. Biomarkers in Clinical Trials: General Principles for Study Design and Statistical Evaluation with Case Studies	9. The Prevention and Treatment of Missing Data in Clinical Trials

Workshop 1
Essentials of Randomized Clinical Trials

This full-day pre-conference workshop is an overview of some essential concepts related to the design, conduct and analysis of clinical trials. The workshop is intended for those with little previous experience or formal training in clinical trials as well as those who have some basic clinical trial experience but desire a better fundamental understanding of the methodological principles and concepts involved in clinical trials. No prior knowledge of biostatistics is needed. The first half of the workshop will introduce participants to some key principles associated with the design and conduct of clinical trials. Topics to be covered include the rationale for randomized clinical trials, key design and methodological issues, such as choice of eligibility criteria, control group, randomization and blinding-related issues, and how to define objectives and end-points for a trial. This first part of the workshop will cover basic principles of data collection, reporting, and quality control as well as principles of project management. The second half of the workshop will provide an overview of statistical principles and methodologies commonly utilized in clinical trials. Topics to be covered include choice of endpoints, sample size computation, methods for treatment allocation and stratification, intent to treat, procedures on how to monitor a trial, and how to analyze the results from randomized clinical trials.

Attendees should be able to describe the essential elements of a clinical trial, essential principles of project management of a multicenter clinical trial, describe key statistical concepts and their application to the validity and interpretation of clinical trial results, and use this knowledge to contribute as a researcher or collaborator in the successful conduct of a clinical trial. In addition, attendees should be able to read clinical trials literature critically.

Faculty: Dixie J. Ecklund, University of Iowa
Susan Halabi, Duke University
Laura Lovato, Wake Forest University
Michele Melia, Jaeb Center for Health Research
Yves Rosenberg, National Heart, Lung, and Blood Institute/NIH

Workshop
Organizer: Yves Rosenberg, National Heart, Lung, and Blood Institute/NIH

Workshop 2
Trial and Site Management for Multi-Center Trials

Effective trial and site management is critical to the successful and timely completion of multi-center clinical trials. This workshop will present information on how this can be achieved. Practical examples will be presented for each topic and discussion with workshop participants will be encouraged.

Our international workshop faculty members have experience in coordinating national and international publicly funded and industry trials, as well as recruiting patients and managing activities at clinical centers. They have worked in a variety of settings and will bring their varied experiences to this workshop.

Participants will leave with a practical overview of trial and site management, tools, resources and ideas for effective trial implementation.

Topics to be covered include:

- Feasibility and site selection
- Study start-up considerations, including paperwork required from sites to participate
- Handling payments to the sites, including different types of contracts
- Establishing study procedures
- Staffing requirements at the coordinating centre
- Training and continuing education of staff at the clinical sites, including information the coordinating centre should provide
- Techniques for interacting effectively with clinical sites and study partners
- Staff motivation at clinical sites
- Patient recruitment and retention strategies
- Data collection systems and techniques to ensure timely reporting
- Quality assurance
- Tracking study metrics
- Study record keeping suggestions
- Study close down process
- Publication arrangements and policies with clinical sites

Faculty: Marie Benavente, University of British Columbia
Lauren McGurk, Rho, Inc.
Beverly Koski, Independent Consultant
Alison McDonald, University of Aberdeen

Workshop
Organizer: Alison McDonald, University of Aberdeen

Workshop 3
Practical Statistical Reasoning in Clinical Trials for Non-Statisticians

This workshop is not an introduction to clinical trials. In fact, it assumes knowledge of and experience in clinical trials. Nor is it an introduction to biostatistics. It does not teach *how* to perform statistical tasks; there are no formulas and no proofs. Instead, it explains *why* these statistical tasks are performed and *what* they mean once they are performed.

This workshop walks you through the clinical trial cycle from beginning to end, and addresses statistical issues discussed between the non-statistician and the biostatistician during that cycle. It starts with the research question and ends with the publication of results. Intermediate topics include:

- Trial design, e.g. basic types of design, primary outcome measure(s), sample size calculation and power analysis.
- Analysis plan, e.g. simple vs. complex statistical models, the use of covariates, longitudinal (repeated measures) models, handling missing data.
- Trial monitoring and Data and Safety Monitoring Board reports, e.g. interim analyses, sample size re-calculation.
- Final analysis, e.g. what do “reject H_0 ” and “do not reject H_0 ” mean? What does the “p-value” mean? Why “correct” for multiple tests? What does “site-by-treatment interaction” mean?
- Subgroup analyses.

Objectives:

- (1) To put in plain English the reasoning and intuition behind basic statistical concepts used in clinical trials.
- (2) To improve communication between non-statisticians involved in clinical trials and their biostatisticians.

Target Audience: Non-statisticians with experience in clinical trials who seek a better understanding of statistical concepts encountered throughout the cycle of a clinical trial.

Faculty: Paul Wakim, National Institute on Drug Abuse/NIH

Workshop

Organizer: Paul Wakim, National Institute on Drug Abuse/NIH

Workshop 4 Adaptive Clinical Trials

Adaptive clinical trials—trials in which key design parameters are modified according to prespecified decision rules during the course of the trial in response to accumulating data from the trial—may be more efficient, ethically acceptable and, if properly designed and executed, accurate than traditional designs. However, the design of such trials is inherently more complex than traditional approaches and must precisely define the planned adaptations *a priori*. In addition, simulation has an important role in evaluating the operating characteristics of adaptive trials. The implementation of adaptive trials introduces additional complexities in logistics, data availability, randomization, drug supply, and interactions with the sponsor and independent data and safety monitoring boards (DSMBs). The rapid proliferation of adaptive designs, and inconsistent use of terminology, has created confusion about the similarities and, more importantly, the differences among the techniques. In this session, the presenters with a broad range of experience in the conduct of these trials will address conceptual, statistical, and logistical issues in the design, implementation, and analysis of adaptive clinical trials.

First Dr. Lewis will discuss logistical and practical issues in composition, function, and interactions with all participants in the trial's design and execution and provide an example from a Phase 2 drug trial. He describes the information flow necessary for an efficient trial and rapid and timely adaptations but also to ensure blinding. Then he describes a case where a DMC used prespecified rules developed in conjunction with the sponsor to drop an arm during a dose-finding trial. Dr. Pinheiro will focus on adaptive dose-ranging designs and analysis methods, discussing their motivation and key elements, and describing some of the most common approaches used in practice. He will conclude by discussing the key results and recommendations from the PhRMA Adaptive Dose-Ranging Studies working group. Then Dr. Connor will describe a dual endpoint (efficacy and safety) adaptive Bayesian design of a medical device. This trial design will be used to illustrate how interim data and a Bayesian longitudinal model can be used to calculate predictive probabilities that are used to identify the optimal trial size during the course of the trial.

Attendees should be conversant in the fundamentals of clinical trial design and methodology, but no foundational knowledge of Bayesian statistics or adaptive designs is required. The expected audience is statisticians, clinicians involved in trials, and other clinical trialists interested in adaptive designs. After the course, attendees will understand the role of adaptive trials and possess the foundation for their design, implementation, and interpretation.

Faculty: Jason Connor, Berry Consultants
Roger J. Lewis, Harbor-UCLA Medical Center
Jose Pinheiro, Janssen Pharmaceutical Companies of Johnson & Johnson

Workshop
Organizer: Susan Halabi, Duke University

Workshop 5

Biomarkers in Clinical Trials: General Principles for Study Design and Statistical Evaluation with Case Studies

Despite some publicized setbacks, biomarkers continue to have the potential to greatly improve healthcare, e.g., in drug development, surrogate endpoint evaluation, risk assessment, and early detection. Biomarkers come in many varieties, e.g., genomic, molecular, or clinical. The utility of a biomarker is context dependent. Its credibility depends on the evidential level observed for its intended use. For candidate biomarkers measured by a medical device (e.g., in vitro diagnostic assay), quality of device measurement can be crucial in assessing biomarker utility. Moreover, when a drug relies on a companion diagnostic device to classify patients for drug eligibility, regulatory acceptance of both the drug and device are needed for joint licensure. This half-day short course will provide an overview ranging from types of biomarkers as drug development tools to the need for *in vitro* diagnostic device development and validation. The course outline includes

- Literature overview of biomarker research
- General principles and practical aspects for development of a biomarker as a classifier, a diagnostic, or a surrogate, etc.
- Study designs including merits and limitations
- Statistical analysis issues for drug development versus for device development and validation
- Formal assessment in clinical trials of the clinical utility of a biomarker as predictive, prognostic or adding benefit
- Prospectively planned retrospective analysis in ongoing or completed trials, including when incomplete genomic samples are collected
- Multiplicity issues
- Misclassification issues in randomized controlled trials
- Single-trial and meta-analytic validation
- Appropriate handling of confounding factors
- Handling of missing test results
- Analytical and clinical validation of the diagnostic device
- Bridging from one companion diagnostic to another for the same intended use
- Regulatory considerations for drug versus for device evaluation
- Examples from a variety of clinical areas

The short course consists of four focused presentations:

Session 1: Overview of biomarkers in drug development

Session 2: Overview of surrogate endpoint evaluation in clinical studies

Session 3: Overview of biomarkers in device development

Session 4: Biomarker Trial Designs: Lessons from real trials

Attendees should have an understanding of clinical trials.

Faculty: Sumithra Mandrekar, Mayo Clinic
Geert Molenberghs, University of Hasselt and Katholieke Universiteit Leuven
Gene Pennello, U.S. Food and Drug Administration
Sue-Jane Wang, U.S. Food and Drug Administration

Workshop

Organizer: Li Chen, Amgen
Christopher S. Coffey, University of Iowa

Workshop 6
Challenges and Strategies of Clinical Trial Data Management

This workshop will discuss real-world strategies learned from both industry and academic sectors to solve common and unique challenges related to collecting and managing clinical trial data. Participants are encouraged to bring their own experiences to include in the discussion. Taught from the perspective of experienced data managers and database developers, participants will learn about and discuss problematic areas such as:

- Communication with study team members
- Working with vendors and laboratories
- Choosing the right Data Management System
- Optimizing Case Report Form (CRF) design
- Enhancing clinical trial data quality
- Sharing and submitting information to sponsors, partners, and the FDA
- Data Sharing and access for NIH funded studies
- Regulations surrounding Data Management

This course applies to anyone working in the clinical data management field in pharmaceutical industries, research institutions as well as universities. This course would also benefit anyone who is involved in the planning and preparing of a clinical trial, conducting a clinical trial, or has management responsibility (direct or indirect) for clinical trials.

Faculty: Kris Nelson, EMMES Corporation
Wenle Zhao, PhD, Medical University of South Carolina

Workshop
Organizer: Devin J. Hunt

Workshop 7

CDISC: What are the Standards, How Will They Help, and How to Adapt?

Although the FDA does not mandate submissions follow **C**linical **D**ata **I**nterchange **S**tandards **C**onsortium (**CDISC**) guidelines and standards, it strongly encourages their use. This workshop begins with an overview of CDISC the various standards it promotes. It then takes an in-depth look at some of the more difficult aspects of mapping clinical data to the **S**tudy **D**ata **T**abulation **M**odel (SDTM) standard. We will also look at some of the challenges of doing legacy conversions (putting older studies in a more “up-with-times’ model).

We will also discuss some of the challenges in creating the **A**nalysis **D**ata **M**odel (ADaM) datasets, especially the all-important subject-level analysis dataset (ADSL). We will also discuss CDISC implementation strategies in your organization. Finally, we end the workshop with a panel discussion, focusing on daily “real world” issues that arise while implementing the CDISC guidelines.

The goal of this workshop is to educate attendees about the ever-evolving CDISC guidelines. Among the groups that stand to benefit from an understanding of the standards are: study coordinators and PI’s responsible for collection of the data at the research site; data managers, programmers, and statisticians who standardize, tabulate, and analyze the data; PI’s and statisticians responsible for traceability between the clinical and analysis datasets; and, of course, the FDA reviewer. Effective standards implementation by these groups reduces delivery time and increases product quality throughout the study life cycle.

Faculty: Jeff Abolafia, Rho, Inc.
 Carol Baker, Rho, Inc.
 Karen Wade, Rho, Inc.
 Rob Woolson, Rho, Inc.

Workshop
Organizer: Carol Baker, Rho, Inc.

Workshop 8
Statistical Procedures for Interim Analysis in Clinical Trials

There are two basic statistical procedures in monitoring of clinical trials: conditional power and group sequential methods. For conditional power evaluation, we will cover the case when the underlying stochastic process follows a discrete Brownian motion process with a linear drift. Predictive power, the Bayesian version of conditional power, will also be presented with discussion. For the topic on group sequential methods, we will start with the classical “constant boundary” approach (Pocock 1977, O’Brien-Fleming 1979 and Wang-Tsiatis 1987) where, for a given alpha value, number of looks and the shape of the boundary, there is an unique corresponding constant determining the desired group sequential boundary. We will continue to introduce a more flexible alpha-spending approach to group sequential methods. Examples will be demonstrated by the use of free software created at University of Wisconsin-Madison.

Design of survival trials design will also be covered. We will present a heuristic introduction to the logrank test which is locally most powerful under proportional hazards assumption. The most popular methods for the comparisons of two survival distributions are the Kaplan-Meier curve and the logrank test. When the proportional hazards assumption is violated, we will demonstrate that these two methods might deliver quite different messages and lead to misleading interpretations.

This workshop provides a primer to the following book: Proschan MA, Lan KKG and Wittes JT. (2006) *Statistical Monitoring of Clinical Trials – A Unified Approach*, Springer.

Faculty: K. K. Gordon Lan, Janssen Pharmaceutical Companies of Johnson & Johnson
Jose Pinheiro, Janssen Pharmaceutical Companies of Johnson & Johnson
Michael Proschan, National Institute of Allergy and Infectious Diseases/NIH

Workshop
Organizer: Susan Halabi, Duke University

Workshop 9
The Prevention and Treatment of Missing Data in Clinical Trials

At the request of the U.S. Food and Drug Administration, the National Academy of Sciences convened the Panel on the Handling of Missing Data in Clinical Trials to prepare a report that would make recommendations that could be used to aid in the FDA's eventual development of a Guidance for Industry on that topic. This half day workshop presents an overview of the findings and recommendations of the resultant report from the perspective of two clinical trialist members of the NAS panel. The workshop will follow the basic organization of the NAS report, though it will place greatest emphasis on aspects of trial design and trial conduct that can be used to minimize issues arising from missing data. However, because trial protocols must also describe how any missing data will be handled at the end of the study, methods for analysis of clinical trial results will be discussed at a conceptual level. We will focus more on the common features of such analyses, than on the technical details of particular analytic methods. To that end, the target audience for this workshop includes biostatisticians and epidemiologists involved in the design of clinical trials, as well as study coordinators and CRAs involved in the conduct of the studies.

We first review settings in which missing data commonly arise and pose difficult problems in the analysis and interpretation of clinical trial results, as a basis for discussing aspects of clinical trial design that could minimize or even eliminate the most troublesome missing data. In particular we focus on aspects of clinical trial design that relate to appropriate definition of primary endpoints, anticipating problems that might arise when patients drop off study drug due to adverse events, lack of efficacy, or competing risks such as newly developed contraindications to therapy or deaths from other causes. We further consider alternative trial designs that would facilitate randomized comparisons among patients who can adhere to protocol defined treatment strategies.

We then consider aspects of trial conduct that will promote the collection and analysis of complete data on all randomized subjects. Proper attention should be paid to informing both investigators and participants of the scientific importance of complete data collection. We describe ways in which the Study Protocol, the Manual of Operations, and the Case Report Forms can facilitate the investigators' understanding of and adherence to the actions that must be taken to minimize missing data, as well as discussing the impact that careful subject education (including the Informed Consent documents) can have on preserving the scientific and statistical relevance of clinical trial results.

Major recommendations of the Panel also included the need for lead investigators to anticipate missing data and to plan for appropriate methods for the statistical analysis of the clinical trial results. We briefly discuss the need for easily understood and clearly described methods based on reasonable assumptions about the mechanisms giving rise to missing data and assumptions about the likely impact that missingness would have on conclusions drawn from the RCT. We give a broad, non-technical overview of some of the approaches that might be used for the primary analysis of the trial results. Then, owing to the impossibility of ever knowing that assumptions about missing data mechanisms are valid, we conclude with an overview of general criteria that should be met by sensitivity analyses that explore the potential impact of the assumptions about missing data.

Faculty: Scott S. Emerson, University of Washington
 James D. Neaton, University of Minnesota

Workshop
Organizer: Rick Chappell, University of Wisconsin