

Statistical Issues for Medical Devices and Diagnostics

Marriott Gaithersburg Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, MD

April 29 - 30, 2009

Sponsored by AdvaMed and FDA-CDRH

Wednesday, April 29

8:30 – 9:00 **CONTINENTAL BREAKFAST**

9:00 – 9:15 **Welcome:** *Tom Maeder, Executive Director, MTLI, AdvaMed*
Gregory Campbell, Division of Biostatistics, CDRH, FDA

9:15 – 10:45 **Bayesian Trial Design and Analysis**
Session planners: Telba Irony, Chief, General & Surgical Devices
Branch, Div. of Biostatistics, CDRH
David Snead, Medtronic CardioVascular

The use of Bayesian methods in design and analysis of medical device clinical trials for submission to FDA has increased considerably in recent years. Bayesian methods are particularly helpful in the medical device arena, not only because of the availability of prior information, but because they offer flexibility with respect to interim analyses, prediction, meta-analysis, and missing data. FDA is also currently exploring the use of formal Decision Analysis methodology which is inherent to the Bayesian approach. Presentations in this session discuss the designs and techniques that have been successfully used in FDA applications, highlight the peculiar problems and solutions for implementation of such techniques in the regulatory setting, and summarize what is presently happening at CDRH.

9:15 – 9:35 **Bayesian Adaptive Clinical Trials: The Beauty of Bayesian Prediction**
Speaker: Andy Mugglin, Research Associate Professor, Div. of
Biostatistics, Univ. of Minnesota, and Statistical Consultant & Founder,
Paradigm Biostatistics, LLC

9:35 – 9:55 **Bayesian Statistics in Medical Device Clinical Trials**
Speaker: Donald Berry, Head, Division of Quantitative Sciences, M.D.
Anderson Cancer Center

9:55 – 10:15 **Bayesian Statistics for Designing and Analyzing Medical Device**
Clinical Trials in the Regulatory Setting
Speaker: Telba Irony, Chief, General & Surgical Devices Branch, Div. of
Biostatistics, CDRH

10:15 – 10:45 Panel Discussion on Bayesian Trial Design

Speakers: All session speakers

10:45 – 11:00

BREAK

11:00 – 12:30

Adaptive Sample Size Re-Estimation

*Session planners: Yonghong Gao, Mathematical Statistician, DBS, CDRH
John Evans, Senior Biostatistics Manager, Boston Scientific*

Session Chair: Richard Chiacchierini, Chiacchierini & Associates

This session focuses on the many ways in which one can use adaptive sample size re-estimation to “right-size” a clinical trial.

11:00 - 11:15 Conditional Power and Sample Size Re-Estimation in a Time-to-Event Setting

Speaker: Joseph Massaro, Senior Statistical Consultant, HCRI, and Associate Professor, Dept. of Biostatistics, Boston University

11:15 - 11:30 Drug-Eluting Stents: A Case Study in Designing an Adaptive Group-Sequential Survival Trial

Speaker: Yannis Jemai, Senior Biostatistician, Cytel, Inc.

11:30 – 11:45 Some Remarks on Non-Fixed Sample Size Design

Speaker: Heng Li, Team Leader, DBS, CDRH

11:45 - 12:00 Some Logistical Considerations in the Implementation of Interim Analysis

Speaker: Dennis W. King, President & CEO, STATKING Consulting, Inc.

12:00 – 12:30 Panel Discussion on Adaptive Sample Size Re-Estimation

Speakers: All session speakers

12:30 – 2:00

LUNCH

2:00 – 3:20

Multiple Secondary Endpoints

*Session planners: Jianxiong (George) Chu, Mathematical Statistician, DBS, CDRH
Michael Lu, Assoc. Director, Biostatistics & Data Management, Edwards Lifesciences*

In clinical trials, a secondary endpoint mainly serves a supportive role to help gain a broader understanding of treatment effect (e.g. mode of device action), and thus findings based on these endpoints do not generally lead to labeling claims. It is, however, now not uncommon for sponsors to seek some endpoint-specific labeling claims from the multiple secondary endpoints, which raises the issue of multiplicity. In this session, two experienced industry speakers will examine various statistical strategies, both frequentist and Bayesian, related to testing multiple secondary endpoints with the appropriate adjustment, followed by a presentation from FDA's regulatory perspective.

Roseann White, Director, Global Biostatistics,
Clinical Data & Systems, Abbott Vascular

Patient-reported outcome (PRO) provides evidence of a treatment benefit from the patient perspective and may be used to support claims in approved product labeling in many therapeutic areas. However, the claims should be derived from adequate and well-controlled studies with reliable and validated PRO instruments. This session deals with the challenges of designing trials with PRO as the primary or key secondary endpoint and issues to be considered when analyzing these types of data.

9:00 - 9:15 Using Patient-Reported Outcomes as Primary or Key Secondary Endpoints in Clinical Trials – a Regulatory Perspective

Speaker: Shiling Ruan, Mathematical Statistician, DBS, CDRH

9:15 - 9:30 Interpreting Health Status and Quality of Life Outcomes

Speaker: Philip Jones, Senior Biostatistician II, Saint Luke's Mid-America Heart Institute

9:30 – 9:45 The Good, the Bad, and the Ugly in Patient Self-Assessments in Seriously Debilitated Patients

Speaker: Richard Chiacchierini, Chiacchierini & Associates

9:45 – 10:00 Issues When Analyzing Patient-Reported Outcome Data

Speaker: Terri Johnson, Mathematical Statistician, DBS, CDRH

10:00 - 10:20 Panel Discussion on Patient-Reported Outcomes

Panelists: All session speakers

10:20 – 10:40 BREAK

10:40 – 12:00 *In Vivo* Diagnostics

*Session Planners: Lakshmi Vishnuvajjala, Chief, Diagnostic Devices Branch, Division of Biostatistics, CDRH
Kristen Meier, Mathematical Statistician, DBS, CDRH*

In vivo diagnostics differ from *in vitro* diagnostics in that they deal with patients rather than specimens. For this reason, they usually involve risk to the patient, unlike the *in vitro* diagnostics. This session addresses statistical issues associated with diagnostic devices.

10:40 - 11:00 Statistical Issues with Clinical Studies of *In Vivo* Imaging Systems: Cervical Imaging as an Aid During Colposcopy

Speaker: Gene Pennello, Team Leader, DBS, CDRH

11:00 - 11:20 Defining Success Issues in Statistical Analysis of *In Vivo* Diagnostics

Speaker: Ramses Sadek, Consultant

11:20 - 11:40 Diagnostic Issues for Cardiovascular Devices

Speaker: Shanti Gomatam, Mathematical Statistician, DBS, CDRH

11:40 - 12:00 Panel Discussion on *In Vivo* Diagnostics

Panelists: All session speakers

12:00 – 1:00 LUNCH

NOTE: The two afternoon sessions are run as parallel tracks

1:00 – 5:00

Statistical Issues in Diagnostics and Imaging

Diagnostic devices differ from therapeutic devices mainly in that they diagnose a condition rather than treat it. The following two sessions deal with personalized medicine and the pre-IDE process. Personalized medicine is a fast-developing area and one of FDA's critical path initiatives. Since most in vitro diagnostic devices do not require an IDE, the pre-IDE process is very important. This session includes both industry and FDA perspectives.

Part A Combining Diagnostics and Therapy

*Session Organizers: Vicki Petrides, Statistician Section Head, Diagnostic Division, Abbott Laboratories
Betty Stephenson, Director, Corporate Statistics & Clinical Data Management, BD*

Drug-diagnostic combinations are at the heart of personalized medicine. This area is the subject of bills proposed by Congress and the HHS Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) draft report. The report recommends FDA's risk-based approach and establishing an entity to assess clinical utility of genetic tests. Drug-diagnostic combinations are also part of FDA's Critical Path Initiative.

Regulatory Issues in Drug-Diagnostic Combinations: a Diagnostic Perspective

Speaker: Lakshmi Vishnuvajjala, Chief, Diagnostic Devices Branch, Division of Biostatistics, CDRH

Practical Issues in the Study of Prognostic or Predictive Genetic Markers: the *KIF6* Arg Variant and its Relationship to Heart Disease and Statin Treatment

Speaker: Charles Rowland, Director, Statistical Genetics, Celera

Identification and Evaluation of Predictive Composite Biomarkers

Speaker: V. Devanarayan, Director, Exploratory Statistics, Global Pharmaceutical R&D, Abbott Laboratories

Part B *In Vitro* Diagnostics: Expert Panel on Pre-IDE Guidance for Laboratory Tests

*Session Organizers: Lakshmi Vishnuvajjala, Chief, Diagnostic Devices Branch, Division of Biostatistics, CDRH
Vicki Petrides, Statistician Section Head, Diagnostic Division, Abbott Laboratories
Paula Johnson, Manager, Clinical Data Management & Statistics, BD*

*Speakers: Carolyn Carroll, Stat Tech, Inc.
Susan Gawel, Statistician, Diagnostics Division, Abbott Laboratories
Betty Stephenson, Director, Corporate Statistics & Clinical Data Management, BD
Kristen Meier, Mathematical Statistician, DBS, CDRH*

Description: The pre-IDE (Investigational Device Exemption) process is an informal exchange between the sponsor and the FDA to review plans for designing and/or conducting studies and analyzing the data prior to formal submission of the results to the agency. This process is a collaborative approach intended to save both the sponsor and the FDA time and money by clarifying study expectations well in advance. This panel of experts will discuss their views, present a case study, and answer questions regarding their experience with the pre-IDE process as it applies to *in vitro* diagnostic devices.

1:00 – 5:00

Postmarket Statistical Issues

Part A

Non-Randomized Trials

*Session Organizers: Gene Pennello, Team Leader, DBS, CDRH
Shelby Li, Principal Statistician, Medtronic Cardiac
Rhythm Disease Management*

This session explores what can and cannot be done statistically in the analysis of non-randomized trials and, in particular, what needs to be pre-specified and how to handle *post hoc* analyses.

Establishing Performance Goals for Continuous Endpoints: Blood Pressure Reduction after Renal Stenting

Speaker: Michael Pencina, Boston University

Study Design and Analysis Issues with Electrical Fetal Monitoring: Computer Assisted Detection Devices

Speaker: Bipasa Biswas, Mathematical Statistician, DBS, CDRH

Application of Causal Inference Methods to Non-Randomized Device Trials

Speaker: Mark Van der Laan, UC Berkeley

Part B

Safety Surveillance

*Session Organizers: Gene Pennello, Team Leader, DBS, CDRH
Joe Bero, Senior Biostatistics Manager, Boston
Scientific*

Safety signal detection, particularly of rare events in the postmarket phase, is particularly challenging for those whose products are not used as widely as others or whose treated population is highly heterogeneous and differs from that studied during the approval phase. This session examines current techniques being used by the agency and by industry to identify safety signals as early as possible.

Current FDA Postmarket Surveillance Strategies for Medical Devices

Speaker: Heshu Duggirala, Epidemiologist, DEPI, CDRH

Bayesian Models for Postmarket Safety Data that Incorporates Drug Class and Medical Event Hierarchy Information

Speaker: William DuMouchel, Phase Forward Lincoln Safety Group

Statistical Strategies for Postmarket Surveillance of Medical Devices

*Speaker: Sharon-Lise T. Normand, Dept. of Health Care Policy,
Harvard Medical School*

5:00

ADJOURNMENT