



3rd Annual FDA/MTLI Medical Device and IVD Statistical Issues Workshop

Gaylord National Hotel
National Harbor, MD
April 28-29, 2010

Wednesday, April 28th

8:30 – 9:00 **REGISTRATION AND CONTINENTAL BREAKFAST**

9:00 **Welcome**

9:00 - 10:30 **Non- Inferiority Session**

9:00 – 9:20 **Development of Non-inferiority Trials: An Industry Perspective**
Joe Bero, Senior Manager, Biostatistics, Boston Scientific

- This presentation will cover relevant issues to be addressed when designing and analyzing non-inferiority trials. Challenges faced by industry to design non-inferiority trials, specifically the choice of the non-inferiority margin, sample sizes and the type 1 error will be addressed. It will cover several case studies designed to illustrate the concept and to identify the changes in methods which occurred over time. Analysis consideration will also be examined based upon findings identified in final analyses of the trials.

9:20 – 9:40 **Outcome-based Biases and Other Issues Involving Non-inferiority Trials**

Mark Rothmann, Ph.D., Team Leader, DBV/OB/CDER

- There are many factors and pitfalls involving the design, analysis, and conduct of non-inferiority trials, including the estimation of the active control effect in the setting of the non-inferiority trial. This presentation discusses the various issues in the design, analysis and conduct of non-inferiority trials with emphasis on recognizing and potentially dealing with conditional biases associated with the estimation of the active control effect.

- 9:40 – 10:00 **Challenges in Non-inferiority Medical Device Clinical Studies: A Regulatory Perspective**
Lilly Yue, Ph.D., Deputy Division Director, DBS/CDRH
- Non-inferiority study design has been widely used in clinical trials for drugs, medical devices and biological products. Apparently, there are many challenges in study design, conduct and analysis as well as regulatory issues. However, the special nature of medical device clinical studies presents unique challenges in designing and evaluating such studies. In this talk, some critical issues will be discussed and illustrated through examples from a regulatory perspective.
- 10:00 – 10:30 **Panel Discussion on Non-Inferiority Issues**
- 10:30 – 10:45 **BREAK**
- 10:45 – 12:15 **Bayesian Statistics Session**
- 10:45 – 11:05 *Jim Rogers, PhD, Principal Statistician, Metrum Research Group (Metrum Institute),*
- Presentation description
- 11:05 – 11:25 *Lurdes Inoue, Associate Professor, Biostatistics, University of Washington*
- Presentation description
- 11:25 – 11:45 *Telba Irony, Ph.D., Branch Chief, CDRH/DBS/GSDB*
- Presentation description
- 11:45 – 12:15 **Panel Discussion on Bayesian Statistics**
- 12:15 – 1:45 **LUNCH**
- 1:45 – 3:15 **Blinding Session**
- 1:45 – 2:05 *Mitzan Mekel-Bobrov, Ph.D., Sr. Biostatistical Scientist, Neuromodulation, Boston Scientific Corporation*
- Presentation description
- 2:05 – 2:25 *Heejung Bang, Ph.D., Associate Professor, Division of Biostatistics & Epidemiology Department of Public Health, Weill Medical College of Cornell University*
- There is strong consensus in the clinical trial community that blinding is an important issue in randomized controlled trials. At present grossly incomplete reporting of procedures and the use of any assessment for blinding still prevails. The term ‘double-blind’ has almost become a convention without any checks or balances. Also there is a lack of consensus on quantitative procedures for evaluating the success of blinding in the literature. In this talk, we

review statistical methods of blinding assessment and discuss some of the most pressing issues surrounding the acquisition, interpretation, and reporting of blinding data. Additional issues and challenges in non-pharmacological studies (e.g., medical device) will be discussed as well.

- 2:25 – 2:45 *Alvin Van Orden, M.S., Mathematical Statistician, GSDB/DBS/CDRH*
- Blinding is a difficult but important part of the design of medical device trials. Doubts are often raised if the subject can feel the device working or if adverse events tip the subject off as to the treatment being received. Blinding assessments can ease concerns about the effectiveness of the blinding. I will present a case study where the blinding assessment established the effectiveness of the masking. In a trial where the effectiveness of the device was marginal, it was important to establish that the small effect was not a product of the lack of blinding.
- 2:45 – 3:15 **Panel Discussion on Blinding Session**
- 3:15 – 3:30 **BREAK**
- 3:30 – 5:00 **Missing Data Session**
- 3:30 – 3:50 *Yanping Chang, M.S., Medtronic*
- Presentation description
- 3:50 – 4:10 *Joseph Massaro, Ph.D., Department of Mathematics and Statistics, Boston University*
- Presentation description
- 4:10 – 4:30 *Gregory Campbell, Ph.D., Division Director, DBS/CDRH*
- Presentation description
- 4:30 – 5:00 **Panel Discussion on Missing Data Session**
- 5:00 **ADJOURNMENT**
- 5:00 – 6:00 **Reception**
- Thursday, April 29th**
- 8:30 – 9:00 **REGISTRATION AND CONTINENTAL BREAKFAST**
- 9:00 – 5:00 **Concurrent Sessions (*Please see following page for today's schedule*)**

5:00

ADJOURNMENT

Note: The today's sessions are run as parallel tracks

TRACK A	Therapeutic Device Track	TRACK B	IVD Track
9:00 – 10:45	Subgroup Analysis: Planning, Conducting and Reporting in Medical Device Trials	9:00 – 11:00	Analytical Studies
9:00 – 9:25	<p><i>Todd Gross, PhD, Senior Director, Biostatistics, Allergan Medical</i></p> <ul style="list-style-type: none"> The Paradox of Subgroup Analysis – A Practical Guide 	9:00 – 9:25	<p><i>Thomas Mathew, Ph.D., Professor, Department of Mathematics and Statistics, University of Maryland Baltimore County</i></p> <ul style="list-style-type: none"> Presentation description
9:25 – 9:45	<p><i>Xiaogang Su, Ph.D., Associate Professor, Biostatistician, Department of Adult Health, SON, University of Alabama at Birmingham</i></p> <ul style="list-style-type: none"> Tree-Structured Subgroup Analysis 	9:25 – 9:45	<p><i>Marina Kondratovich, Ph.D., Associate Director for Clinical Trials, Office of Personalized Medicine, OIVD/CDRH</i></p> <ul style="list-style-type: none"> Presentation description
9:45 – 10:05	<p><i>Chul Ahn, Ph.D., Mathematical Statistician, CODB/DBS/CDRH BA</i></p> <ul style="list-style-type: none"> Reporting Subgroup Analysis Results in SSED 	9:45 – 10:05	<p><i>James Garrett, PhD, Manager of the Bioinformatics, Algorithms, and Non-Clinical Statistics” group, BD Diagnostic Systems</i></p> <ul style="list-style-type: none"> CLSI document EP12-A, "User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline," is frequently applied by FDA reviewers during the approval process. It presents a criterion for reproducibility studies involving a "95% interval" (p. 5). Although the document describes when the criterion is not applicable, it does not suggest alternatives, and therefore is sometimes applied outside its intended use. I discuss this intended use, and demonstrate examples where the criterion seems nonsensical.
10:05 – 10:25	Panel Discussion	10:10 – 10:25	BREAK
10:25 – 10:40	BREAK	10:25 – 10:45	<i>Vicky Petrides, Abbott</i>

- Presentation

10:40 – 12:10 **Patient Reported Outcomes**

10:45 – 11:00 **Panel Discussion**

10:40 – 11:00 *Jeff Sloan, Ph.D., Professor, Oncology and Biostatistics, Dept. Health Sciences Research, Mayo Clinic*

11:00 – 12:10 **Communication**

- Presentation description

11:00 – 11:20 *Kristen Van Dole, Ph.D., Epidemiologist, Office of Surveillance and Biometrics, FDA/CDRH*

11:00 – 11:15 *Betty Stephenson, M.S., Director, Corporate Statistics & Clinical Data Management, BD*
“When Guidance becomes Gospel”

- Presentation description

11:20 – 11:40 *Richard Chiacchierini, Ph.D., R.P. Chiacchierini & Associates*

11:15 – 11:35 *Elliot Cowan, Ph.D. Branch Chief, DETTD/OBRR/CBER*

- Presentation description

- Presentation description

11:40 – 12:10 **Panel Discussion**

11:35 – 11:55 *Estelle Russek-Cohen, Ph.D., Deputy Division Director, DB/OBE/CBER*

- Presentation description

11:55 – 12:10 **Panel Discussion**

12:10 – 1:10 **LUNCH**

12:10 – 1:10 **LUNCH**

1:10 – 2:40 **Risk Benefit Analysis**

1:10 – 2:40 **Biomarkers**

1:10 - 1:30 *Melissa Simones, Boston Scientific*
Risk-benefit Evaluation in Cardiac Resynchronization Therapy Trials

1:10 - 1:30 *Abha Sharma, Ph.D, Roche Molecular Systems*

- This presentation provides an industry perspective of risk-benefit evaluation, specifically in cardiac resynchronization therapy trials. An over view of cardiac resynchronization therapy will be

- Presentation description

presented along with specific examples of risk benefit assessment. Both statistical and practical considerations in approaching risk benefit will be discussed.

1:30 – 1:50 *Roger Lewis, Ph.D., UCLA*

- Presentation description

1:30 – 1:50 *Michael Pencina, Ph.D., Harvard Clinical Research Institute*
Steve Skates

- Presentation description

1:50 – 2:10 *Xuefeng Li, Mathematical Statistician, PhD, CDRH/DBS/GSDB*

- Presentation description

1:50 – 2:10 *Steve Skates, Ph.D., Harvard Medical School*

- Presentation description

2:10 – 2:40 **Panel Discussion**

2:10 – 2:30 *Yuying Jin, Ph.D. Mathematical Statistician, DDB/DBS/CDRH*

- Presentation description

2:40 – 3:55 Communication

2:30 – 2:40 Open Discussion

2:40 – 3:05 *Peggy Pereda, Boston Scientific*

- Communication between FDA and Industry Statisticians: an Industry Perspective

During this session, participants will have the opportunity to raise topics and questions of interest for open discussion by the group.

We will capture discussion points during the session and post them with the meeting presentations.

3:05 – 3:30 *Gary Kamer, M.S. Mathematical Statistician, CODB/DBS/CDRH*

- Presentation description

3:30 – 3:55 **Panel Discussion**



3:55 – 4:10 BREAK
4:10 – 5:00 OPEN DISCUSSION
5:00 ADJOURNMENT

3:55 – 4:10 BREAK
4:10 – 5:00 OPEN DISCUSSION (continued)
5:00 ADJOURNMENT

Important Notice

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