



11th Annual FDA/AdvaMed Medical Devices & Diagnostics Statistical Issues Conference

Washington Marriott at Metro Center | Washington, DC
May 9 – 10, 2018

Wednesday, May 9, 2018

- 8:45 – 9:15 am** **Registration Check-In and Breakfast**
- 9:15 – 9:20 am** **Welcome and Introduction of Keynote Speaker**
2018 Conference Co-Chairs: Yun-Ling Xu, *FDA, CDRH* and Victoria Petrides, *Abbott*
Ram Tawari, *FDA, CDRH*
- 9:20 – 10:00 am** **Keynote Address**
Jeffrey Shuren, *MD, FDA*
- 10:00 – 10:30 am** **Break**
- 10:30 – 12:00 am** **What’s New in Medical Device Development**

Co-organizers:

James Lesko, *Medtronic*
Liz Galle, *CVRx*
Jie Zhou, *FDA, CDRH*
Jincao Wu, *FDA, CDRH*

Speakers/Panelists

Ram C. Tiwari, *FDA, CDRH*
Carol Mansfield, *RTI*
Li Wei, *Chinese Academy of Medical Sciences*

Developments in the health care industry and advances in medical device technology often lead to new regulatory requirements and alternate forms of evidence generation. Guidelines from different authorities are often complementary, but there are differences that manufacturers should understand in order to stay competitive internationally. In this session, speakers will discuss new FDA guidance documents and CDRH priorities, as well as regulations and guidelines in other regions. The utility and appetite for patient preference data continues to grow, along with the methods for analyzing such data. Developments in the collection and use of patient preference data as part of an evidence generation strategy will also be discussed.

- 12:00 – 1:30 pm** **Lunch**
- 1:30 – 3:00 pm** **Utilizing Real World Evidence in Medical Device Evaluation**

Co-organizers:

Chithra Sangli, *Johnson & Johnson*
Charles Gordon, *LivaNova*
Changhong Song, *FDA, CDRH*
Nelson Lu, *FDA, CDRH*

Speakers:

Lilly Yue, *FDA, CDRH*
Sharon-Lise Normand, *Harvard*
Nirav Dalal, *Abbott*
Greg Campbell, *GCStat Consulting LLC*

Real world evidence (RWE) yielded from real world data (RWD) are playing an increasingly important role in enhancing the evaluation of the safety and effectiveness of medical devices. The use of RWD can potentially reduce the cost and duration of clinical trials while providing more generalizable evidence. Appropriate statistical methods must be used in order to draw reliable statistical inferences and maintain scientific validity. This session focuses on the practical aspects of incorporating RWE including case studies. Following presentations, there will be a panel discussion amongst the FDA, academic and industry participants.

3:00 – 3:30 pm

Break

3:30 – 5:00 pm

On the use of statistical significance vs clinical significance

Co-organizers:

Tim Hanson, *Medtronic*
Mailin Hesse, *Abbott*
Arianna Simonetti, *FDA, CDRH*
Xin Fang, *FDA, CDRH*

Speakers:

Ted Lystig, *Medtronic*
Lakshmi Vishnuvajjala, *FDA, CDRH*
Alicia Toledano, *Biostatistics Consulting, LLC*
Martin Ho, *FDA, CDRH*

This session will present the current thinking on the fundamental topic: statistical significance vs. clinical significance. The statistical significance is expected to show that a random variable is different from its comparator at a certain significant level, while the clinical significance reveals that the performance of a test device provides a relevant clinical meaningful effect either at an individual or at a population level. Because almost every summary measure from a trial is a random observation, a well-designed trial should take into consideration both statistical and clinical significance. In regulatory setting, clinical research data analyzed with statistical methods focus on pre-specified hypotheses and the associated tests to avoid data dredging, which promotes the decision to be made on unconfirmed hypotheses. Although clinical decisions are based on more than one aspect, the pertinent clinical significance should not be random and should be pre-specified in the protocol as well. Given statistical significance and clinical significance may need each other, our speakers and panelists will share their perspectives on the topic and its current use in clinical trial design and decision making.

5:00 – 6:00 pm

Poster Session and Networking Reception

Co-sponsored by the American Statistical Association's Medical Device and Diagnostics Section

Thursday, May 10, 2018

8:15 – 8:45 am

Breakfast

8:45 – 4:30 pm

Concurrent Sessions - Therapeutic Device Track and Diagnostics Track

Therapeutic Device Track

8:45 – 9:00 am	Welcome Yun-Ling Xu, <i>FDA, CDRH</i>
9:00 – 10:30 pm	Multiple Endpoint-specific Labeling Claims in the Presence of Composite Primary Endpoint <u>Co-organizers:</u> Michael Lu, <i>Edwards Life Sciences</i> Rajesh Nair, <i>FDA, CDRH</i> <u>Speakers:</u> Andrew Mugglin, <i>University of Minnesota</i> Zengri Wang, <i>Medtronic</i> Ja-An Lin, <i>FDA, CDRH</i> Multiple endpoints for labeling claims in the presence of composite primary endpoint is a common practice in medical device clinical trials. The selection of the endpoints for labeling claims, specifications of the test hypotheses for each endpoint, methods and strategies to control the overall type I error are all important considerations for the study design and analysis outcome presentations. In this session, we will present and discuss these topics from scientific, regulatory, and practical perspectives.
10:30 – 10:45 pm	Break
10:45 – 12:15 pm	Applying the Least Burdensome Principles to Clinical Study Designs <u>Co-organizers:</u> Shelley-Ann Walters (3M) Hong Lu (FDA, CDRH) <u>Speakers:</u> Laura Hatfield (Harvard University) Zhen Zhang (Abbott Vascular) Xu Yan (FDA, CDRH) “Least burdensome” is the minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time. Although well-controlled, randomized clinical trials are highly desirable in demonstrating safety and effectiveness of medical devices, this approach may not be the least burdensome approach when there are historical data available for related device and control. This session will provide an overview of the range of clinical study designs and statistical analyses that applied least burdensome principles to reduce the burden of resources to obtaining necessary evidence for regulatory approval or clearance.
12:15 – 1:15 pm	Lunch
1:15 – 2:45 pm	Statistical Analysis of Multiple Data Sources <u>Co-organizers:</u> Pei Li (Medtronic) Ying Yang (FDA, CDRH) <u>Speakers:</u> Vandana Mukhi (FDA, CDRH) Lanyu Lei (Medtronic) Charles Gordon (LivaNova)

Under the right conditions and using proper statistical methods, data from multiple sources (e.g., OUS (Out of US) data, post-market surveillance, same study conducted in multiple regions, etc.) can be used to better understand the benefit-risk profile of devices used in clinical care and support regulatory decision-making, including potentially generating valid scientific evidence. Since not all studies are conducted under the same protocol and patient population may not be the same, simply pooling all datasets together without considering the heterogeneity among the datasets will not provide valid causal inferences between medical device exposures and outcomes. In this session, speakers will discuss the challenges and different strategies in analyzing data from multiple sources. Examples of using post-market study data to support expansion of the indications for use of an approved device will be presented.

2:45 – 3:00 pm

Break

3:00 – 4:30 pm

Choice of Estimands and Sensitivity Analyses

Co-organizers:

Theodore Lystig (Medtronic)
Peter Lam (Boston Scientific)
Vandana Mukhi (FDA, CDRH)

Speakers:

Kalyanee V Appanna (Novartis)
Daniel Scharfstein (Johns Hopkins University, Bloomberg School of Public Health)
Heng Li (FDA, CDRH)

When designing randomized controlled clinical trial, it is important to clearly define what is to be estimated or the estimand of interest. The trial objective should be linked to a precise definition of the treatment effect that is to be estimated. Approaches to assess robustness of the results through sensitivity analysis should be aligned to the estimand. In this session, speakers will discuss through examples the choice of estimands and sensitivity analyses considered in medical device clinical trials. They will also provide insight into the Addendum to the ICH E9 guidance document in the context of device trials.

4:30 pm

Adjournment

Diagnostics Track

8:45 – 9:00 am

Welcome

Victoria Petrides, Abbott

9:00 – 10:30 pm

Analytical Studies for Diagnostic Tests - Standards Update and Case Studies

Co-organizers:

Darcy Vavrek, *Illumina*
Lan Huang *FDA, CDRH*

Speakers:

Jeffrey Budd, *Beckman Coulter*
Marina V. Kondratovich, *FDA, CDRH*
Kristen Meier, *Illumina*
Tinghui Yu, *FDA, CDRH*

For diagnostic devices, establishment of analytical performance is a critical step in development and for product labeling. There are many different types of studies that are performed in order to characterize the different aspects of device performance including

but not limited to precision, method comparison, bias estimation, linearity, and spiking/dilution recovery. While consensus standards exist for these studies, existing standards do not always address the study design and statistical analysis challenges brought with new technologies. This session will provide updates on some CLSI Evaluation Protocols revisions in progress, highlight related statistical issues and provide case examples for evaluating the performance of quantitative and qualitative diagnostic tests. The session will conclude with a short panel discussion.

10:30 – 10:45 pm

Break

10:45 – 12:15 pm

Statistical Considerations and Development for Precision (Repeatability and Reproducibility) Studies

Co-organizers:

Bin Sun, *Roche*
Wei Wang, *FDA, CDRH*

Speakers:

Meijuan Li, *FDA, CDRH*
Leonard Buchner, *Biostatistician Consultant*
Christoph Berding, *Roche Diagnostics*

Precision refers to the closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions. For diagnostic assays, the precision experiment is performed to estimate the imprecision or random error of the analytical method. The precision studies mainly evaluate two aspects, repeatability and reproducibility. Traditionally, repeatability was evaluated by processing aliquots from the same sample under a set of repeatability conditions and reproducibility was evaluated by processing aliquots from the same sample under different condition by varying one or multiple factors at a time. With the development of new technologies such as PCR assays, NGS assays and point of care devices, there are challenges in both experimental design and statistical analysis regarding the precision studies. In this session, we will discuss the precision study design for capillary samples, precision study analysis for PCR assays, and different crossed vs. nested designs in the precision studies.

12:15 – 1:15 pm

Lunch

1:15 – 2:45 pm

Statistical Issues in Agreement Studies and Assessment of Reader Agreement

Co-organizers:

Angel De Guzman, *Abbott*
Xuan Ye, *FDA, CDRH*

Speakers:

Lawrence Lin, *JBS Consulting Services Inc.*
Bipasa Biswas, *FDA, CDRH*
Liansheng Larry Tang, *George Mason University*

Agreement studies assess the agreement of two measurement methods, e.g., two diagnostic devices. In a 510(k) submission, the new device should be demonstrated to be substantially equivalent to a legally marketed predicate device. The agreement study can evaluate and establish substantial equivalence for a new measurement method or diagnostic device with quantitative or qualitative outputs. For devices that require reader's interpretation, reader agreement is important. Statistical methods to evaluate reader agreement determine the magnitude of agreement between or among readers. These analyses commonly focus on the reliability of evaluations between different readers or in the same reader on different occasions. This session will discuss statistical issues in Agreement studies and the assessment of Reader Agreement.

2:45 – 3:00 pm

Break

3:00 – 4:30 pm

Precision Medicine – Statistical challenges

Co-organizers:

Minh-Thien Vu, *Abbott*

Yaji Xu, *FDA,CDRH*

Speakers:

Gene Pennello, *FDA, CDRH*

Yuanyuan Xiao, *Gilead*

Jill Walker, *AstraZeneca*

When it comes to patients' care, the physician wishes to have a personalized treatment for this patient. It requires not only an understanding of the biological, anatomical and physiological mechanisms of the disease, but also of the complex intersection of environmental, genetic, social and cultural factors. Yet, the ability to identify patients most likely to benefit from a given treatment from those who will incur cost and suffer side effects without gaining benefit is critical. This is so called 'personalized medicine'. In this session, we will focus on what we have learned about precision medicine devices and how can we move the field forward. Examples of topics are:

- Cutting-edge technologies for precision medicine
- Novel statistical methods in ranking and selection different expressed genes
- Statistical methods in normalization to extract biologically relevant information from microarray data.'

4:30 pm

Adjournment