12th Annual FDA/AdvaMed Medical Devices & Diagnostics Statistical Issues Conference

Washington Marriott at Metro Center | Washington, DC
April 24 – 25, 2019

Wednesday, April 24, 2019

8:45 – 9:15 am **Registration Check-In and Breakfast**

9:15 – 9:20 am **Welcome and Introduction of Keynote Speaker**

9:20 – 10:00 am **Keynote Address**
Sherri Rose, Harvard Medical School

10:00 – 10:30 am **Break**

10:30 – 12:00 pm **An Approach for Incorporating Real-World Evidence into Regulatory Decision-Making**

Co-organizers:
Vandana Mukhi, *FDA, CDRH*
Arianna Simonetti, *FDA, CDRH*
Minglei Lei, *Medtronic*
Ge Guo, *Roche*
David Stivers, *Hologic*

Speaker
Lilly Q. Yue, *CDRH/FDA*

Panelists
Lilly Q. Yue, *CDRH/FDA*
Gene Pennello, *CDRH/FDA*
Alicia Toledano, *Biostatistics Consulting, LLC*
Priscilla Velentgas, *Aetion*

Recent advances in biomedical science have made available a considerate amount of high–quality Real-World Data (RWD) that can be used in support of scientific evidence for healthcare and regulatory decision-making. This session will focus on a novel statistical methodology that has been developed to leverage RWD into regulatory decision-making. The proposed approach uses a proven analytical method of propensity score to stratify pre-selected RWD patients - whose covariates' profiles are similar to those found in patients from the current study - and current study patients into homogeneous strata. Frequentist and Bayesian methods are then applied to make inference. Our speaker will provide an in-depth understanding of the new methodology followed by panel discussion.

12:00 – 1:30 pm **Lunch**

1:30 – 3:00 pm **Sensitivity Analysis for Unmeasured Confounding in Observational Studies**

Co-organizers:
Ying Yang, *FDA*
Jessie Moon, *FDA*
Robert Neher, *Zimmer Biomet*
Kristen Meier, *Illumina*

Speaker
Maya Mathur, *Harvard University*

Discussants
Yun-Ling Xu, *FDA/CDRH*
Peter Lam, *Boston Scientific*

Observational studies are a common type of study for evaluating medical devices and diagnostic products. Due to the non-randomized nature of observational studies, the absence of confounding cannot be assumed when the associations between a given exposure and a given outcome are investigated. The failure to account for confounding in the study design and statistical analysis methods can lead to biased results and ultimately an incorrect inference. Meanwhile, observational studies and statistical models rely on assumptions, which can range from how a variable is defined or summarized to how a statistical model is chosen and parameterized. The validity of all inferences from any analysis is dependent upon the extent to which these assumptions are met. Any violation of the necessary assumptions can result in bias caused by systematic error, i.e. error that cannot be reduced by increasing the number of observation units. In this session, speakers will discuss sensitivity analysis techniques that could be used to quantify the effect of an unmeasured confounder and evaluate robustness of results.

3:00 – 3:30 pm **Break**

3:30 – 5:00 pm **Precision Medicine / Benefit-Risk Assessment for Therapeutic and Diagnostic Devices**

Co-organizers:
Chul Ahn, *FDA*
Wei Wang, *FDA*
Chithra Sangli, *J&J*
Janel Huang, *Abbott*

Speakers:
Meijuan Li, *CDRH/FDA*
Lan Huang, *CDRH/FDA*
Paul Coplan, *Johnson & Johnson*

Precision medicine or personalized medicine indicates a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. 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 in precision medicine. In this session, we will discuss the impact of misclassification of patients on the targeted therapy efficacy based on the predictive biomarker measurement using the companion diagnostic device (CDx) which can also be understood as benefit/risk assessment for CDx of precision medicine. We will also discuss a new benefit/risk measure by incorporating information about true positive and true negative cases (correct diagnosis) and false positive and false negative cases (incorrect diagnosis) for facilitating the necessary decision making. In addition, a case study on benefit-risk assessment for a therapeutic device will be presented.

5:00 – 6:00 pm **Poster Session and Networking Reception**

Thursday, April 25, 2019

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**

9:00 – 10:30 am **Considerations for External Evidence Fusion in Medical Device Trials**

Co-organizers:
Rajesh Nair, *FDA*
Graeme Hickey, *Medtronic*

Speakers:
Theodore Lystig, *Medtronic*
Brian Hobbs, *Cleveland Clinic*
Xuefeng Li, *FDA*

Traditionally, regulatory decision making for medical devices has relied on prospective clinical trials, whether for pre- or post-market studies, with trial data being analyzed in isolation. There is a now a plethora of external data sources that can be exploited to supplement prospective clinical studies. These external data sources can derive from numerous sources, including electronic health records, clinical registries, administrative databases, historical clinical or feasibility studies, computational or simulation data, and expert elicitations. The ability to augment prospective clinical studies with external evidence can potentially lead to smaller, more efficient clinical trials. However, doing this in a scientifically rigorous manner poses numerous challenges requiring the development of innovative methodology. In this session, speakers will expand on this emerging area and provide examples.

10:30 – 10:45 am **Break**

10:45 – 12:15 pm **Analysis Methods for Recurrent Events**

Co-organizers:
Jack Zhou, *FDA*
Greg Ginn, *Abbott*

Speakers:
Wei-chen Chen, *OSB/CDRH*
Stephan Ogenstad, *Statogen Consulting; Georgia Southern University*

Recurrent events endpoints are often used in clinical trials for medical devices. Recent publications and regulatory filings have indicated an increased interest in the use of statistical methods for the analysis of recurrent events. Some of the methodology is relatively new compared to older statistical models. Identifying the optimal model for use in an analysis maximizes resources and may increase statistical power. The current practice of these models will be discussed along with newer methodologies. It is important that more clinical trialists, statisticians, and regulators get exposed to the most appropriate methodologies for the analysis of recurrent events data in order to reduce time and cost as well as to standardize methodologies where appropriate.

12:15 – 1:15 pm **Lunch**

1:15 – 2:45 pm **Issues in Reporting Composite Endpoints in Medical Device Clinical Trials**

Co-organizers:
Yu (Audrey) Zhao, *FDA*
Divine Ediebah, *Abbott*

Speakers:
Roseann White, *Your Third Opinion*
Greg Campbell, *GCStat Consulting LLC*
Rong Tang, *FDA/CDRH*

Composite endpoint is commonly used in medical device trials to improve the power to detect differences in the primary endpoint. Recently, the use of Finkelstein & Schoenfeld method (1999)- win ratio (Pocock, 2012) approach to deal with various severity degree of the components within a composite endpoint is of increasing interest. In this session, the speakers will share their experiences and view on the implementation, the result interpretation, and the pros and cons of Finkelstein and Schoenfeld -win ratio method in medical device clinical trial setting from different perspectives. The speakers will also touch on the challenges in reporting general composite endpoints and how to mitigate these disadvantages.

2:45 – 3:00 pm **Break**

3:00 – 4:30 pm **Simple Design Vs. Complex Design**

Co-organizers:
Manuela Buzoianu, *FDA*
Pei Li, *Medtronic*

Speakers:
Rajesh R. Nair, *CDRH/FDA*
Kristine Broglio, *Berry Consultants, LLC*
Michael Rosenblum, *Johns Hopkins Bloomberg School of Public Health*

In this session speakers from the FDA, industry and academia talk about methodological advances and challenges with “complex” trial design using either Bayesian or frequentist methods. In particular, compared to “simple” designs, adaptive designs can be more efficient in shortening trial duration by allowing early stopping for futility or effectiveness or can improve the chance of success of an underpowered trial by employing sample size reassessment. Enrichment adaptive designs can be also used to modify the patient population during the study, to restrict it to patients with a more favorable benefit-risk profile. In regulatory setting, complex designs can be helpful for instance in speeding up the assessment and review of breakthrough devices or those going through an expedited access pathway (EAP) for pre-market approval. On the other hand, “complex” adaptive designs may require a lot of hard work upfront, such as extensive simulations, to preplan and to preserve study integrity and validity. They are not always feasible, can introduce operational bias or can inflate type I error rate. Ultimately, the optimal design can be adaptive or non-adaptive depending on the situation, and it can be simple or complex.

4:30 pm **Adjournment**

Diagnostics Track

8:45 – 9:00 am **Welcome**

9:00 – 10:30 am **Software as a Medical Device**

Co-organizers:
Dandan Xu, *FDA*
Kendra Hilson, *Roche*
Khone Saysana, *Roche*

Speakers:
Pat Baird, *Philips*
Xiaoqin Xiong, *FDA/CDRH/OSB*
Vinzent Rolny*, Roche Diagnostics*
Yuqing Tang, *FDA/CDRH/OSB*

Digital health technology is constantly advancing. An innovative class of digital health technology is Software as a Medical Device (SaMD), defined by the International Medical Device Regulators Forum (IMDRF) as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device". Some examples of SaMD are software intended to diagnose a condition using a non-medical device such as a smartphone or software that performs image processing to detect cancer. Just as technology pertinent to SaMD is evolving so are the regulations, policies and standards for developing, evaluating and manufacturing digital health products. This session will further explore software development standards in a newly developing regulatory environment; statistical principles and methods for SaMD e.g. in vitro imaging and digital pathology devices; clinical algorithms and digital biomarkers; and SaMD in vivo diagnostics.

10:30 – 10:45 am **Break**

10:45 – 12:15 pm **Statistical Challenges in The Evaluation of Monitoring Devices**

Co-organizers:
Qin Li, *FDA*
Linye Song, *FDA/CBER*
Angel DeGuzman, *Abbott*

Speakers:
Zhiheng Xu, *FDA*
Feiming Chen, *FDA*
Zoe Welsh, *Abbott Diabetes Care*

This session is intended to discuss topics related to longitudinal data, correlation, and false positive/missed detection rates from continuously collected real time temporal data. Speakers from FDA and industry will present data characteristics, analysis challenges and statistical/mathematical methods for such data using examples from monitoring devices (both continuous and event) such as glucose monitor and control devices.

12:15 – 1:15 pm **Lunch**

1:15 – 2:45 pm **Diagnostic Devices with Non-binary Diagnostic Classifiers**

Co-organizers:
Manasi Sheth-Chandra, *FDA*
Nicholas Burn, *Abbott*

Speakers:
Bipasa Biswas, *FDA*
Marina Kondratovich, *FDA*
Vicki Petrides, *Abbott Laboratories*

Dichotomization of medical diagnostic tests, where only decisions for or against the presence of the target condition are used, sometimes provides no information about the inconclusive test results. However, in some cases, a "gray zone" or intermediate zone or nominal/ordinal/semi-quantitative classification is incorporated, resulting in more than two results. Using such zones or classification, a kX2 table is more appropriate than ignoring the test scores in these zones/classifications. However, if medical professionals cannot utilize the additional information provided by the conditional operating characteristics in order to decide effective patient management, then the kx2 table would potentially serve limited purpose.

2:45 – 3:00 pm **Break**

3:00 – 4:30 pm **Applications of Artificial Intelligence and Machine Learning in Diagnostics**

Co-organizers:
Yaji Xu, *FDA*
David Stivers, *Hologic*

Speakers:
Sumit Chopra, *Imagen Technologies*
Peter Costa, *Hologic, Inc.*
Chava Zibman, *FDA/CDRH*

Ongoing rapid development of artificial intelligent (AI) analytical methods applicable to large scale data sets and image collections (i.e., 'big data') such as machine learning and deep learning make their application to the healthcare setting attractive. AI has the potential to reveal clinically relevant information from a massive amount of healthcare data. It also has the potential to assist decision making in clinical practice. The US Food and Drug Administration (FDA) published the guidance "Software as a Medical Device (SAMD): Clinical Evaluation" in 2017, and in 2018, permitted marketing of a medical device using a series of deep learning detectors to search for lesions specific to diabetic retinopathy. This session will provide topics from both industrial and regulatory perspectives, exploring recent AI development in healthcare with an emphasis on diagnostics.

4:30 pm **Adjournment**