14th Annual FDA/AdvaMed Medical Device Statistical Issues Conference

Virtual Event

May 11 – 13, 2022

Wednesday, May 11, 2022

11:00 am – 11:05 am **Welcome and Introduction of Keynote Speaker**

11:05 am – 11:45 am **Keynote Address**
Scott Evans, Professor and Founding Chair, Department of Biostatistics Bioinformatics; Director, George Washington Biostatistics Center

11:45 am – 11:50 am **Break**

11:50 am – 12:50 pm **What's New in Medical Device Development**
The impact of the FDA and industry in health care and medical device development continues to broaden and evolve. In this session, the FDA will discuss CDRH priorities and initiatives, such as guidance documents and guidelines, as well as the challenges and opportunities in statistical innovation that help facilitate innovation in medical device development and regulatory decision-making. Next, industry speakers will address novel statistical approaches for handling the impact of COVID-19 and prevalence-based clinical site selection using an automated Microsoft Power BI Dashboard in medical device clinical studies. Finally, industry will discuss the role of statistics in data science in the tech company setting, and how collaboration can be achieved between biostatisticians and data scientists.

Co-organizers
Mourad Atlas, FDA
Elysia Garcia, FDA
Kara Keller, Abbott
Trina Patel, Edwards Lifesciences

Speakers
Martin Ho, Google
Sharon Schneider, Abbott
Peter Lam, Boston Scientific
Lilly Yue, FDA

12:50 pm – 12:55 pm **Break**

12:55 pm – 1:55 pm **Estimand**
The ICH E9 (R1) addendum provided the foundation of estimand dealing with intercurrent events, especially for handling missing data. One facet of

estimand that is not discussed in ICH E9 (R1) but is crucial in the context of observational studies, namely propensity score weighting for covariate balance, will be presented. How weighting schemes are connected to estimand, or more specifically to one of its five attributes identified in ICH E9 (R1), the attribute of population, is illustrated using the Rubin Causal Model. Three propensity score weighting schemes are examined from practical perspectives.

Two case studies where patient follow up visits were impacted by the COVID-19 pandemic will be shared and discussed. The first one is a device management trial in improving health outcome in heart failure patients utilizing the pre-specified sensitivity analysis addressing the estimand of treatment benefit during the pre-COVID period in contrast to treatment benefit observed after the onset of the pandemic. The second one is an infant growth monitoring trial where subject visits were impacted by clinical site lockdown after the onset of the pandemic. The study team proactively amended the protocol allowing visit window extension, parent reported measurement data, virtual visits, and specifying a statistical approach including sensitivity analyses to address the impact of these intercurrent events.

Co-organizers
Sherry Liu, FDA
Ge Feng, FDA
Peter Lam, Boston Scientific
Angel DeGuzman, Abbott Diagnostics

Speakers
Heng Li, FDA
John Henderson, Abbott Medical Device
Geraldine E. Baggs, Abbott Laboratories

1:55 pm – 2:00 pm **Break**

2:00 pm – 3:00 pm **Statistical Considerations and Methods to Utilize Real World Evidence in Medical Device Evaluation**

Real world evidence (RWE) leveraged from real world data (RWD) is playing an increasingly important role in enhancing the evaluation of the safety and effectiveness of medical devices. Different sources of external data and statistical methods may be incorporated in the design and analysis of clinical studies in support of regulatory decision-making for the approval/clearance of new devices, or expansion of the indications for use of those already marketed. These data and methods may also reduce the duration of clinical trials and provide evidence that is more generalizable.

When using RWD to generate RWE for regulatory decision-making, there needs to be confidence in the validity of such evidence. Therefore, appropriate statistical methods should be employed to make reliable inferences and to maintain scientific validity. In this session, speakers and panelists will discuss case studies that highlight study design and statistical considerations to generate robust RWE, including practical examples for both therapeutic and diagnostic devices.

Co-organizers
Tianyu Bai, FDA
Arianna Simonetti, FDA

Jaron Arbet, UCLA Jonsson Comprehensive Cancer Center
Crystal Williams, Roche

Speakers
Nelson Lu, FDA
Gregory Campbell, GCStat Consulting, LLC

Panelists
Yun-Ling Xu, FDA
Elodie Baumfeld Andre, Roche

3:00 pm – 3:05 pm **Break**

3:05 pm – 4:35 pm **Poster Session**

Thursday, May 12, 2022 – Therapeutic Devices

11:00 am – 11:10 am **Welcome Remarks**

11:10 am – 12:10 pm **Propensity Score Methods**
Many clinical studies nowadays incorporate Real-Worlds Data (RWD) and historical controls as conducting a prospective studies such as a Randomized Controlled Trial (RCT) require tremendous costs and time. However, this will lead an imbalance between two treatment groups as subjects from different data sources have different demographic and characteristics, and these confounding factors may induce bias in the clinical study. To overcome this, propensity score methods are widely used to balance the treatment and control groups so that the clinical trial resembles a randomized trial. In this session, speakers will discuss contemporary issues on propensity score methods. Contemporary issues include an augmentation of clinical trials using external/historical controls, propensity score methods in regulatory submissions, and propensity score matching for three treatment groups. Speakers will present their contributions on these topics in the session.

Co-organizers
Brandon Park, FDA
Michael Lu, Edwards Lifesciences

Speakers
Wei-Chen Chen, FDA
Zengri Wang, Medtronic
Jaron Arbet, UCLA Jonsson Comprehensive Cancer Center

12:10 pm – 12:15 pm **Break**

12:15 pm – 1:15 pm **Use of Predictive Probability in Adaptive Design**
The predictive probabilities have been frequently used in Bayesian adaptive designs for futility interim monitoring of clinical trials and, in some settings, for efficacy monitoring. Given interim data, they can assess how likely a trial is to achieve its objective to yield a statistically significant treatment effect at some future sample size and, in particular, at the final analysis when the trial would reach its maximum sample size (Saville et al, Clin Trials 2014). A recent approach, the Bayesian Goldilocks design (Broglio et al, JBS 2014) postulates its application to perform sample size adaptations where the

interim enrollment decision rule is based on the predictive probability of study success. It also allows for complete follow-up of all patients before the actual primary analysis is conducted. Different models, such as the beta-binomial and piecewise exponential models, as well as simulation-based methods are used in practice to facilitate the implementation of those designs and, in particular, the predictive probability calculations. In this session, we will discuss some case studies of Bayesian adaptive trial designs utilizing predictive probabilities from industry and regulatory perspectives.

Co-organizers
Manuela Buzoianu, FDA
Qian Ren, Abbott

Speakers
Andrew Mugglin, Paradigm Biostatistics; University of Minnesota
Xuefeng Li, FDA
Ben Saville, Berry Consultants

1:15 pm – 1:20 pm **Break**

1:20 pm – 2:20 pm **Beyond the Cox Model and Log-Rank Test: Recent Advances in Survival Analysis for Clinical Trials**

Clinical trials of therapeutic devices commonly report time-to-event event outcomes. In many of these trials, the "standard" approach is to analyze the time to first event only, with comparisons between treatment groups evaluated using log-rank tests or Cox proportional hazards regression models. At the same time, for some trials, recurrent events or multiple events, perhaps with different level of clinical importance, may be more relevant, and valuable information otherwise discarded if simpler endpoints and/or analyses are used. Moreover, where a simple time-to-event analysis is appropriate, model assumptions such as proportional hazards might be violated, leading to unreliable findings. To address these challenges, a plethora of innovative statistical approaches have been proposed in recent years. This session explores some of these methods, including joint frailty models, restricted mean survival time (RMST), Finkelstein-Schoenfeld method, win ratio, etc. In this session, the speakers will review some of these innovations.

Co-organizers
Yu (Audrey) Zhao, FDA
Graeme Hickey, BD

Speakers
Yu Shu, Abbott Medical Devices
Rong Tang, FDA
LJ Wei, Harvard University

2:20 pm – 2:25 pm **Break**

2:25 pm – 3:25 pm **Multiple Testing and Multiple Endpoints in the Context of Adaptive Designs**

Adaptive designs allow for more efficient and flexible clinical trials, where mid-course designs adaptions can be made based on interim data without compromising the overall Type I error rate. In this session, speakers will discuss strategies to address challenges in multiple testing in multi-arm and

multi-stage group sequential design, and in the context of designs with multiple endpoints. Adjusting for multiplicity is critical in adaptive clinical trial designs. In their presentations, speakers will elaborate on how the family wise type 1 error will be controlled in these contexts. The session will conclude with a discussion.

Co-organizers
Adrijo Chakraborty, FDA
Anna Liza Antonio, Edwards Lifesciences

Speakers
Cyrus Mehta, Cytel, Inc.
Li Ming Dong, FDA

3:25 pm – 3:30 pm **Break**

3:30 pm – 4:30 pm **Poster Session**

Friday, May 13, 2022 – Diagnostic Devices

11:00 am – 11:10 am **Welcome Remarks**

11:10 am – 12:10 pm **Study Design Challenges Related to Enrollment, Enrichment and Endpoints in Diagnostics Studies**
Designing a clinical study for evaluating diagnostic devices is different from that for evaluating therapeutic devices. Even within the diagnostic device evaluation, the study design can vary for different devices and different indications for use. Appropriate pivotal study design depends on when the device is used, how it is used and who will use it, etc. In this session, we will discuss several common problems and the challenges one can face when designing the clinical study in the regulatory setting. Specifically, we will discuss design issues related to study enrichment in companion diagnostics (CDx) clinical validation studies. The challenges in evaluating guided tumor tissue detection device will also be presented.

Co-organizers
Yuqing (Elaine) Tang, FDA
Joanne Lin, Illumina

Speakers
Qin Li, FDA
Johan Surtihadi, Illumina
Arianna Simonetti, FDA

12:10 pm – 12:15 pm **Break**

12:15 pm – 1:15 pm **Evaluation of Complex Biomarkers**
Challenges with study designs and analyses of diagnostic tests often involve more than one/single analyte or biomarker. For example, In Vitro Diagnostic Multivariate Index Assays (IVDMIA) combines the values of multiple variables, liquid biopsy test includes multiple genes, variants and variant types. Complex biomarkers may also include genomic signatures as microsatellite instability (MSI) and tumor mutation burdens (TMB) and etc. The analytical and clinical validation for these complex biomarkers can be

different from single analyte/biomarker validations, which can create various challenges for study designs and statistical analyses. Liquid biopsy-based tests using circulating tumor DNA/cell-free DNA (ctDNA/cfDNA) are developing rapidly and are being applied in precision medicine through companion diagnostics (CDx). Liquid biopsy tests also face their own challenges in study designs and analyses, e.g., detection of non-tumor associated Clonal hematopoiesis of indeterminate potential (CHIP) variants in limit of blank (LoB) study. In this session, we will discuss the methods and challenges when evaluating such complex biomarkers.

Co-organizers
Xiaoqin Xiong, FDA
Mailin Hesse, Abbott

Speakers
Changhong Song, FDA
Laura Yee, National Cancer Institute
Kevin D'Auria, Guardant Health

1:15 pm – 1:20 pm **Break**

1:20 pm – 2:20 pm **What's New for Software as a Medical Device (SaMD)**
While software has been a key component of medical devices for many years, the use of software as a medical device (SaMD) is more recent. Most of us are familiar with frequent updates required for our smart phones, but what are the implications when an update is needed for a SaMD product? What issues need to be considered to protect against cybersecurity threats? How do you validate a SaMD product? Speakers from the FDA and industry will share case studies and recommendations to address these questions and more.

Co-organizers
Jessie Moon, FDA
Vicki Petrides, Abbott

Speakers
David Peters, Abbott Laboratories
Feras Hatib, Edwards Lifesciences
Feiming Chen, FDA

2:20 pm – 2:25 pm **Break**

2:25 pm – 3:25 pm **Developments in Analytical Studies (CLSI, Other guidelines)**
Analytical studies are integral components in diagnostic device developments and labeling. They are utilized to characterize various aspects of device performance. In this session, we will provide some updates on CLSI guidance such as EP12 and summarize current recommended study designs for Sample Community Study/Contrived Sample Functional Characterization Study.

Co-organizers
Guangxing (Ken) Wang, FDA
Ho-Hsiang Wu, FDA
Hsi-Wen Liao, Illumina

Speakers
Marina Kondratovich, FDA
Wei Wang, FDA
Jesper Johansen, Radiometer Medical ApS
Derek Blythe, Illumina

3:25 pm – 3:30 pm **Break**

3:30 pm - 4:00 pm **Poster Session**