15th Annual FDA/AdvaMed Medical Device Statistical Issues Conference

Grant Hyatt Washington | Washington, D.C.
May 11-12, 2023

Thursday, May 11 – Independence (5B)

8:45 – 9:15 am **Registration Check-In and Breakfast – Independence Foyer (5B)**

9:15 – 9:20 am **Welcome and Introduction of Keynote Speaker**
Opening remarks from FDA/AdvaMed Conference Steering Committee Co-Chairs: Joanne Lin, Illumina, Inc. and Lu (Laura) Hong, FDA
Introduction of Keynote Speaker: Gregory Alexander, Director, Division of Biostatistics, FDA

9:20 – 10:00 am **Keynote Address**
Jennifer Jones-McMeans, Ph.D., Divisional Vice President, Global Clinical Affairs, Abbott Vascular, Inc.

10:00 – 10:30 am **Break**

10:30 – 12:00 pm **External Evidence in the Evaluation of Medical Devices**
The use of real-world evidence (RWE) extracted from real-world data (RWD) is becoming increasingly important in improving the assessment of medical device safety and effectiveness. Various external data sources and statistical methods can be integrated into the study design and analysis of clinical trials to aid regulatory decision-making for the approval or clearance of new devices, as well as expanding the indications for existing devices. During this session, speakers and panelists from industry and regulatory agency will be invited to share their practical experience and considerations in the following topics.:

a. The utilization of hybrid data (e.g., RWD, external data such as investigator-initiated study, historical control, sample collection, literature review, along with the clinical trial data) or external data alone in the regulatory submission, such as the establishment of the reference intervals or performance goal derived by indirect methods

b. Innovative Methods to Augment Trials Leveraging Real-world Data (RWD)

c. Harmonization of endpoint definition across different sources of data
d. Successful or unsuccessful stories using external evidence in the submission
e. How to overcome the challenge when data privacy impacts the quality of the external evidence (e.g., for long-term follow-up, the data privacy may create more missing data or bias)

Co-organizers
Tianyu Bai, FDA
Saryet Kucukemiroglu, FDA
Feng Tang, Medtronic
Xiao Yu, Edwards Lifesciences

Speakers
Bo Lu, The Ohio State University
Lilly Yue, FDA
Zengri Wang, Medtronic

12:00 – 1:30 pm **Lunch - Independence (5B)**

1:30 – 3:00 pm **Methods of AI/Machine Learning for Medical Devices**

Artificial Intelligence (AI) and Machine-Learning (ML) algorithms have been increasingly used in the medical field, often in the form of Software as a Medical Device (SaMD) or Software in a Medical Device (SiMD). In this session we discuss AI/ML-related topics of general interests, including considerations for Pre-determined Change Control Plans for AI/ML, the review standard of the analytical and clinical performance of products involving AI/ML algorithms (e.g., for monitoring purpose or diagnostics purposes), and the use of AI to help predict the outcome of a trial before it happens or to analyze the outcome of the trial.

Co-organizers
Mourad Atlas, FDA
Feiming Chen, FDA
Charles Gordon, Livanova
Jingye Wang, Illumina, Inc.

Speakers
Daniel Goldenholz, Beth Israel Deaconess Medical Center
Vinay Pai, FDA
Frank Samuelson, FDA

3:00 – 3:30 pm **Break**

3:30 – 5:00 pm **Dialogue with the New FDA/CDRH Biostatistics Division Director, Dr. Gregory Alexander**

The session will consist of a dialogue between the FDA/CDRH biostatistics division leaders and industry senior managers to discuss the latest directions and challenges in the evaluation of diagnostic and therapeutic devices. Dr. Gregory Alexander will open the session with some remarks and join the other panelists to provide perspectives and answer questions submitted in advance as well as engage interactively with the audience.

Co-organizers
Cristiana Mayer, Johnson & Johnson Vision
Vicki Petrides, Abbott, Inc.
Arianna Simonetti, FDA
Jack Zhou, FDA

Speakers
Gregory Alexander, FDA
Hope Knuckles, Abbott, Inc.
Xiao-Yu Song, Johnson & Johnson Vision
Yun-Ling Xu, FDA

5:00 – 5:05 pm **Day 1 Adjournment and Announcement of Poster Session Winner**

AdvaMed Statistical Working Group Co-Chairs:
Vicki Petrides, Abbott, Inc. and Roseann White, Edwards Life Sciences

5:05 – 6:00 pm **Poster Session and Networking Reception - Independence B-E**

Friday, May 12

8:00 – 8:25 am **Breakfast – Independence Foyer (5B)**

8:25 – 4:00 pm **Concurrent Sessions - Therapeutic Device Track and Diagnostics Track**

11:45am - 12:45pm **Lunch – Independence (5B) BCDE**

Remarks from FDA/AdvaMed Conference Steering Committee Co-Chairs: Joanne Lin, Illumina, Inc. and Lu (Laura) Hong, FDA

Therapeutic Device Track – Independence (5B) FG

8:25 – 8:30 am **Welcome**
AdvaMed Statistical Working Group Co-Chair:
Roseann White, Edwards Life Sciences

8:30 – 10:00 am **Statistical Issues in Designing Innovative Adaptive Clinical Trials**

In recent years, adaptive designs in clinical research have attracted much attention because it offers not only the flexibility for identifying potential clinical benefit of a medical device under investigation, but also the efficiency for speeding up the development process. Possible adaptations to the trial design include sample size re-estimation, stopping early for futility or success and dropping a treatment arm or population enrichment, etc. In this session, speakers will discuss the statistical methods and challenges in designing Bayesian adaptive design, illustrate successful case examples using both Bayesian and frequentist adaptive approach in the marketing application, and discuss the strength and limitations of Bayesian approach and its decision rules from the regulatory perspective.

Co-organizers
Kan Shang, Edwards Lifesciences
Yu-te Wu, FDA

Speakers
Manuela Buzoianu, FDA
Peter Lam, Boston Scientific
Bonnie Zhang, Edwards Lifesciences

10:00 – 10:15 am **Break**

10:15 – 11:45 am **Statistical Considerations for Utilizing RWD/RWE in Complex Study Designs**

Complex and innovative study designs are often attractive for reducing sample size and lowering the cost and duration of a study. Such designs often incorporate real world data and evidence (RWD/RWE) and may involve either Bayesian or non-Bayesian methods. Other possibilities for potentially stopping a study early include the utilization of an intermediate study endpoint as a surrogate for the final study endpoint, to then be followed with a final analysis at the end of the study. In this session speakers will

discuss these types of study designs and the potential for their use in regulatory submissions.

Co-organizers
Feiran Jiao, FDA
Jim Lesko, DePuy Synthes

Speakers
Paul Coplan, Johnson & Johnson
Amy Crawford, Berry Consultants
Nelson Lu, FDA

11:45 – 12:45 pm **Lunch - Independence (5B) BCDE**

12:45 – 2:15 pm **Challenges with the Pandemic – What Now?**

Though the Biden administration is set to declare an official end to the COVID-19 public health emergency this May, that does not mean that this is the end of the COVID-19 public health emergency's impact on the US population. Whether it's the very long-term effects of the virus, its variants or its vaccines OR the impact of delaying treatment requiring hospitalization, OR the developmental and mental health issues for children OR the continued use of tele-medicine and decentralized healthcare OR the reduction or elimination of some Medicare/Medicaid health benefits after May 2023, the impacts will be felt for many years to come. Essentially, with the end of the public health emergency, we now have three types of environments impacting participants during a clinical trial: pre-emergency, during the emergency and after the emergency. This has implications for trial design and analysis planning from what data do we use for our assumptions, to how to adjust for bias, increased variability and missing data under the changing conditions and the impact of decentralized trials.

Co-organizers
Rhoda Muse, FDA
Roseann White, Edwards Lifesciences

Speakers
Joe Marion, Berry Consultants
Robin Sutherland, Onxeo S.A.
Bram Zuckerman, FDA

2:15 – 2:30 pm **Break**

2:30 – 4:00 pm **Covariate Adjustment and Subgroup Analysis**

Recent statistical advances for covariate adjustment in clinical trial design and analysis show some benefit in improving the precision and power of clinical trials by adjusting for pre-specified, prognostic baseline variables such as age, gender and comorbidities. This would result in a reduction of sample size and more efficient trial design. This session aims to discuss when statistical methods for covariate adjustment may be useful and how to implement them. The session is also planned to discuss how to assess and interpret study results in the presence of heterogeneity across subgroups given by patient baseline characteristics in a randomized clinical trial.

Co-organizers
Adrijo Chakraborty, FDA
Elmira Torabzadeh, Illumina, Inc.

Speakers
Jim Lesko, DePuy Synthes
Michael Rosenblum, Johns Hopkins University
Daniel Rubin, CDER/FDA

4:00 pm **Adjournment**

Diagnostics Track – Independence (5B) HI

8:25 – 8:30 am **Welcome**

AdvaMed Statistical Working Group Co-Chair:
Vicki Petrides, Abbott, Inc.

8:30 – 10:00 am **The Analytical Bridging Study or Migration Study and Its Study Design, Acceptance Criteria, and Statistical Analysis**

Assay bridging or migration is often required during the product's lifecycle. One imminent example is the transition from Illumina's HiSeq platform to the NovaSeq platform for NGS assays used for patient enrollments. CLSI EP09 guidance provides a general framework, yet challenges may be unique to each study such as how the current guidance should fit the next-generation sequencing platform or NGS based assay (e.g. assay migration study for CDx), how the qualitative assay bridging or migration study should be done differently, how the analysis should focus on the decision point, whether the analysis result should be evaluated by significance or equivalence test and how the acceptance criteria should be justified.

Co-organizers

Kai Qu, FDA
Bonnie Zhang, Edwards Lifesciences

Speakers
Shuguang Huang, Stat4ward
Michelle Sonnenberg, Illumina, Inc.
Changhong Song, FDA
Wei Wang, FDA

10:00 – 10:15 am **Break**

10:15 – 11:45 am **Challenges in Validating Device Output**

Validation is the key to accuracy which underpins the quality of any measure provided by a device - on market, in an investigational setting or as a proof of concept. The challenges at each of these stages in device generation look intrinsically different and unique, this session will give a descriptive take on each of the perspectives when trying to validate device output. Including the challenges we face when investigating an entirely new measure, trying to produce the most accurate device, and trying to challenge device claims to protect the population from in-accurate readings and devices.

Co-organizers
Marcus Riley-Green, Abbott, Inc.
Ken Wang, FDA

Speakers
Chongzhi Di, Fred Hutchinson Cancer Center
Tim Dunn, Abbott, Inc.
Elaine Tang, FDA

11:45 – 12:45 pm **Lunch – Independence (5B) BCDE**

12:45 – 2:15 pm

Statistical Issues/Challenges in the Evaluation of Digital Pathology Devices

Digital pathology devices have emerged in the field of pathology to assist pathologists in analysis of digitized images of slides. Some examples of digital pathology devices include whole slide imaging (WSI) system for automated digital slide creation/viewing and AI/ML based software in the detection of region that are suspicious for cancer during the review of scanned WSI. Several critical questions in the evaluation of digital pathology devices are: How to appropriately design, select performance metrics and plan for statistical analysis in multi-reader-multi-case (MRMC) study? How the agency evaluates and makes approval or clearance determinations given the totality of the evidence? What are the benefit-risk assessment criteria for a diagnostics product? In this session, we will share regulatory and industry perspectives in several statistical issues/challenges in the evaluation of digital pathology devices.

Co-organizers
Mark Holland, Beckman Coulter
Jihye Park, FDA

Speakers
Weijie Chen, FDA
Robert Magari, Beckman Coulter
Dandan Xu, FDA

2:15 – 2:30 pm **Break**

2:30 – 4:00 pm

Latest Standards Revisions and Guidance Documents in Analytical Studies, and the Applicability to the Newest Technology, such as Next-Generation Sequencing Test

Analytical studies are used in diagnostic device development to characterize various aspects of device performance. These studies are designed and conducted according to recommendations provided in guidance documents such as the CLSI EP. In this session, proposed best practices for contrived sample characterization study design and analysis will be presented, CLSI EP25-A Evaluation for Stability will be discussed and updates on other CLSI guidance will be provided.

Co-organizers
Ge Feng, FDA
Linye Song, CBER/FDA
Michelle Sonnenberg, Illumina, Inc.

Speakers

Li Guan, Illumina, Inc.
Mark Holland, Beckman Coulter
Marina Kondratovich, FDA
Ho-Hsiang Wu, CBER/FDA

4:00 pm **Adjournment**