FDA/AdvaMed Medical Device Statistical Issues Conference

J.W. Marriott | Washington, D.C.
April 2-3, 2024

Tuesday, April 2

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

9:15 – 10:00 am **Welcome and Keynote Address**

10:00 – 10:30 am **Break**

10:30 – 12:00 pm **In Memory of Dr. Greg Campbell's Contributions to Innovations in Medical Device Statistics**

During his nearly 20-years at the Food and Drug Administration (FDA), Dr. Greg Campbell played an outstanding leadership role in establishing a statistical community of medical devices. He was a founder of the annual FDA/AdvaMed Statistical Workshop established in 2008, and a driving force in the formation of the ASA Special Interest Group for Medical Devices and Diagnostics (MDD), which became an ASA Section on MDD in 2014. To support medical device technology innovation and regulatory decision-making, Dr. Campbell led many initiatives. He was a driving force and an exceptional leader in statistical innovation in the medical device world and in advancing regulatory science. He helped shape the course of medical device evaluation by pioneering Bayesian statistical methodology, causal inference, adaptive design, missing data and diagnostic test methodology, in the regulatory settings. He also spearheaded the efforts in FDA statistical guidance development for medical devices including guidance documents on implementing Bayesian statistics, pivotal clinical trial study design and adaptive designs in regulatory submissions. His pioneering work and sustained efforts have resulted in profound, far-reaching and long-lasting impact on public health, FDA and Industry.

Co-organizers
Rajesh Nair, FDA
Rong Tang, FDA
Jim Lesko, DePuy Syntheses
Zengri Wang, Edwards Lifesciences

12:00 – 1:30 pm **Lunch**

1:30 – 3:00 pm

Continue the Dialogue Between the FDA/CDRH Biostatistics Division Director and Industry: What Are the Challenges and Opportunities in 2024?

This session provides the continuation of the dialogue with the Biostatistics Division Director, Dr. Gregory Alexander, and industry leaders in 2024. Dr. Alexander will open the session with some remarks and join the other panelists to provide perspectives on challenges and opportunities for 2024. The FDA/CDRH biostatistics division leaders and industry senior managers will discuss the latest directions and hot topics in the evaluation of diagnostic and therapeutic devices and answer questions submitted in advance as well as engage interactively with the audience. Of interest,

- *Collaboration and new pieces of guidance e.g. on use of RWD/RWE in regulatory decisions, FDA's perspective on increasing diversity in clinical trials and guidance*
- *Innovation e.g. digital technologies and AI and clever trial designs incorporating different sources of evidence*
- *Envision the future in medical devices, e.g. what are the upcoming challenges and opportunities*

Co-organizers
Manuela Buzoianu, FDA
Elysia Garcia, FDA
Andrea Geistanger, Roche Diagnostics GmbH
Cristiana Mayer, Johnson & Johnson Vision
Khone Saysana, Roche Diagnostics GmbH

3:00 – 3:30 pm **Break**

3:30 – 5:00 pm

Challenges in Validating Free-Living Wearable Measures With an Imperfect or Nonexistent Ground Truth

In light of providing evidence aiding patient-focused drug development, wearable sensor-derived free-living measures have shown promise in providing objective and reliable information on patients' meaningful aspects of health. Before we utilize such measures in clinical trials, appropriate validation is necessary to ensure the measures' accuracy and reliability. However, there are challenges in demonstrating clinical utility and validating some of those wearable sensors-derived measures such as measures tracking Parkinson's disease progression or quantifying depression status based on voice sentiment. During this session, speakers and panelists from industry and regulatory agency will be invited to discuss their experiences and considerations for the following challenges:

- *How to select fit-for-purpose ground truth for validation of measures if ground truth is imperfect or nonexistent;*
- *How to establish these measures' clinical validity if traditional clinical measures are imperfect;*
- *How to determine a clinically important difference in free-living measures.*

Co-organizers
Saryet Kucukemiroglu, FDA
Qing Yin, FDA
Kara Keller, Abbott, Inc.
Sylvia Li, Verily

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

5:05 – 6:00 pm **Poster Session and Networking Reception**

Wednesday, April 3

8:00 – 8:25 am **Breakfast**

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

11:45am -12:45pm **Lunch**

Diagnostic Device Track

8:25 – 8:30 am **Welcome**

8:30 – 10:00 am **Statistical Issues for Genomic or Complex Biomarkers**
Driven by technological innovations in diagnostic medical devices, the complexity of biomarkers continues to evolve rapidly, introducing increasing statistical challenges in designing and analyzing analytical and clinical validation studies. As new knowledge in genomics allows for more targeted treatment of diseases such as cancer, diagnostic medical devices like companion diagnostics (CDx) are increasingly vital tools. Diagnostic assays of circulating tumor DNA (ctDNA) present in the blood of cancer patients are a new and powerful innovation with broad clinical applications. One promising clinical application of ctDNA uses it as an early detection biomarker for an asymptomatic population, especially for cancers with no approved screening methods. Next generation sequencing (NGS) based assays could detect low levels of ctDNA and sequence a subset of

targeted genes or the whole genome. Instead of screening for a single cancer type for traditional screening tests, multi-cancer early detection (MCED) assays can check for many types of cancer from different organ sites at the same time from a single test. This session will cover topics including the companion diagnostic (CDx) bridging study, ctDNA-based assays, MCED, and complex biomarkers.

Co-organizers
Dandan Xu, FDA

10:00 – 10:15 am **Break**

10:15 – 11:45 am **AI/ML Applications and Challenges in the Development of In-Vivo Diagnostic Devices Using AI and ML**

Artificial intelligence (AI) and machine learning (ML) holds the potential to significantly impact various aspects of medical device development and applications including enhancing image processing, patient monitoring, and personalized healthcare solutions. From early disease detection to personalized treatment plans, AI is proving instrumental in optimizing patient outcomes. AI tools offer automation in device development process, leading to enhanced efficiency and reliability in data collection and analysis by managing an iterative process and handling large datasets. Specially, AI technologies are revolutionizing the analysis of medical images, providing quicker and more accurate diagnostic insights. The integration of AI in medical devices and the continuous development of the algorithms also poses challenges, requiring thoughtful consideration of ethical, regulatory, and privacy implications as well as potential biases. This presentation will discuss the study design challenges and case examples in the development of the in-vivo diagnostic device using AI/ML algorithms in training, validation, and modifications.

Co-organizers
Lan Huang, FDA
Aida Yazdanparast, Illumina, Inc.

11:45 – 12:45 pm **Lunch**

12:45 – 2:15 pm **Recent Updates on CLSI Standards and Guidance Documents for Design and Analysis of Medical Device Design Verification and Validation Studies**

Design and analysis of verification and validation studies for diagnostic devices rely on guidance from CLSI standards and

other guidance documents. This session will detail the most recent standards revisions and work in progress, and how to apply them to medical device studies. The session will include an overview of proposed upcoming revisions to CLSI EP17, rationale for changes to EP25 made in ED2 and initial practical application, and discussion of EP39. A brief overview of CLSI document updates will also be provided.

Co-organizers
Ge Feng, FDA
Michelle Sonnenberg, Illumina, Inc.

2:15 – 2:30 pm **Break**

2:30 – 4:00 pm **Quality Statistical Review Checklist for Diagnostic Devices and Best Practices**

The FDA has previously published "Quality Statistical Review Checklist of Investigational Device Exemption (IDE) Submissions for Diagnostic Medical Devices" (Biopharmaceutical session, JSM 2012). As mentioned in the paper, "the Division of Biostatistics (DBS) has developed "IDE checklists" to aid its reviewers in carrying out complete and consistent reviews of IDEs… Such checklists can also be beneficial to statistical counterparts in the device industry by providing transparency regarding FDA's considerations in its statistical review…".
Other FDA guidance documents such as "Design Considerations for Pivotal Clinical Investigations for Medical Devices Guidance for Industry, Clinical Investigators, Institutional Review Boards and FDA Staff" (November 2013), can also be a useful resource for sponsors designing studies for devices. Therefore, this session aims to provide a checklist/guidance for the statistical review of diagnostic device submissions in general and offer best practices from the FDA and industry speakers.

Co-organizers
Kai Qu, FDA
Angel De Guzman, Abbott Inc.

4:00 pm **Adjournment**

Therapeutics Track

8:25 – 8:30 am **Welcome**

8:30 – 10:00 am **Innovative Statistical Approaches for Utilization of Real-World Data in Evaluation of Medical Products**

Innovative statistical methodologies are needed for efficient and appropriate use of real-world data from sources beyond traditional clinical trials for regulatory decision making. Together, real-world data and statistical breakthroughs will help bring safe and effective medical products to patients expeditiously. This session will cover innovative study designs and outcome analyses to improve reliability and relevance of RWE. The title of the first talk is "Leveraging real-world evidence via the hybrid study design when the endpoint is time to event". The topic of the second talk is "Optimization-based techniques for matching and weighting in observational comparative effectiveness research as an alternative to propensity score methods". The third talk is on the National Evaluation System for health Technology Methodology Framework by the lead of the framework workgroup.

Co-organizers
Ying Yang, FDA
Paul Coplan, Johnson & Johnson

10:00 – 10:15 am **Break**

10:15 – 11:45 am **Estimand Framework in Medical Device Trials: Align Statistical Analyses with Clinical Question of Interest**

The ICH E9(R1) addendum on estimands and sensitivity analysis in clinical trials released in 2019 highlights the importance of selecting an appropriate Estimand that aligns with the trial's objective. The structured framework is to strengthen the dialogue between disciplines involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation regarding the treatment effect(s) of interest that a clinical trial should address. In this session, we will discuss the five elements included in the Estimand, i.e. treatment, population, variable, population-level summary, and handling of intercurrent events, in support of the clinical question to be addressed from a statistical perspective.

Co-organizers
Elaine Tang, FDA
Roseann White, Edwards Lifesciences

11:45 – 12:45 pm **Lunch**

12:45 – 2:15 pm **Hierarchical Composite Endpoints: Design Considerations and Statistical Challenges**

A hierarchical composite endpoint (HCE) is a combination of different clinical outcomes ranked based on their clinical importance. These types of endpoints have been widely used in clinical trials over the past decades due to its advantages over the traditional composite endpoints (TCE) in accounting for the clinical importance of each component of the composite endpoints. Even though the history of studying a HCE is relatively shorter than that of a TCE, recently, there has been considerable development on this topic. In this session, the speakers will discuss study design considerations and statistical challenges with the HCE and present statistical methods to analyze the HCEs in clinical trials.

Co-organizers
Adrijo Chakraborty, FDA
Brandon Park, Edwards Lifesciences

2:15 – 2:30 pm **Break**

2:30 – 4:00 pm **Quality Statistical Review Checklist for Therapeutic Devices and Best Practices**

The speakers in this session will address key issues for therapeutics medical devices and best practices while reviewing/submitting an application. Specific topics concerning FDA such as standardizing the structure of statistical analysis plan (SAP) to ensure quality submission. The division of clinical evidence and analysis II (DCEAII) has developed a comprehensive list of items to be visited in an in-depth review of a pre-market application for therapeutic devices. This can be served as a valuable resource for statisticians and discussed in detail. This session will also address how the sponsor is encouraged to work with the FDA statisticians early and closely for a successful study. The presentations will be followed by a panel discussion on these topics.

Co-organizers
Mourad Atlas, FDA
Shuguang Huang, Stat4ward

4:00 pm **Adjournment**