8th Annual FDA/MTLI Medical Device and IVD Statistical Issues Workshop
Westin Crystal City
Arlington, VA
April 29 – 30, 2015

Wednesday, April 29th

8:45 – 9:15  REGISTRATION AND CONTINENTAL BREAKFAST
9:15 – 9:20  Welcome
9:20 – 10:00  **Keynote Address: Increasing the Practicality of Innovative Trial Design**
Speaker: Christopher Coffey, Ph.D., Professor of Biostatistics, The University of Iowa College of Public Health

10:00 – 10:30  BREAK

10:30 – 12:00  **New FDA Guidelines**

*Co-organizers: Haiwen Shi, Mathematical Statistician, CDRH/FDA; Ying Yang, Mathematical Statistician, CDRH/FDA; Jeff Lande, Principal Statistician, CRHF Clinical Statistics, Medtronic; Jennifer Yen, Principal Statistician, Abbott Diagnostics*

*Speakers: Gregory Campbell, Director, Division of Biostatistics, CDRH/FDA; Lakshmi Vishnuvajjala, Chief, Diagnostic Devices Branch, CDRH/FDA; Victoria Petrides, Principal Statistician, Abbott Diagnostics*

In this session, recent guidance documents that are of interest to the statistical community will be discussed. FDA Guidance documents that are published in draft form and some which are to be published may also be discussed. We cover both therapeutic and diagnostic areas. While FDA guidance only represents FDA’s current thinking and not regulation, interaction between FDA, industry and academia always advances public health.

12:00 – 1:30  LUNCH

1:30 – 3:00  **Issues on Registries**

*Co-organizers: Nelson Lu, Mathematical Statistician, CDRH, FDA; Changhong Song, Mathematical Statistician, CDRH, FDA; Theodor Lystig, Distinguished Statistician, Strategic Scientific Operations, Medtronic, Inc.*

*Speakers: Theodor Lystig, Distinguished Statistician, Strategic Scientific Operations, Medtronic, Inc.; Sharon-Lise Normand, Professor, Department of Health Care Policy, Harvard Medical School; Lilly Yue, Deputy Director, Division of Biostatistics, CDRH/FDA*

Data from national/international registries start to play more and more important roles in device evaluation in both pre- and post-market settings. Although the utilization of registry data have some potential benefits, such as reduction in sample size and saving subjects from unnecessary risk during clinical studies, various challenges arise. This session reviews the design of registry for regulatory purpose and the utilization of registry data, and discusses the associated statistical and regulatory challenges on how to obtain reliable statistical inference. Issues, such as assessing endpoints, data quality, etc., will be discussed from both pre- and post-market perspectives.
3:00 – 3:30 BREAK

3:30 – 5:00 Do’s and Don’ts When Preparing Statistics Sections of Submissions

Co-organizers: Rajesh Nair, Mathematical Statistician, CDRH, FDA; Norberto Pantoja-Galicia, Mathematical Statistician, CDRH/FDA; Jim Lesko, Manager, Biostatistics, Depuy Synthes

Speakers: Heng Li, Ph.D, Mathematical Statistician, FDA/CDRH, Alicia Y. Toledano, Sc.D., Owner, Biostatistics Consulting, LLC and Arkendra De, Ph.D., Mathematical Statistician, FDA/CDRH

A key factor for successful pre-market submissions of medical devices and diagnostics is the implementation of sound and clear statistical sections. The speakers in this session, statisticians from industry and FDA with extensive experience in the development and review of pre-market submissions, will discuss the challenges faced by FDA and industry during the review process and provide a framework to aid statisticians and preparers of these documents in deciding what information to include (and not to include) in the statistical sections.

5:00 – 6:00 Reception

Thursday, April 30th

8:30 – 9:00 CONTINENTAL BREAKFAST

9:00 – 5:00 Concurrent Sessions

(Two Parallel Tracks: Therapeutic Device Track and Diagnostics Track)

THERAPEUTIC DEVICE TRACK

9:00 – 10:30 Placebo Effect in Randomized and Non-Randomized Device Trials

Co-organizers: George (Jianxiong) Chu, Mathematical Statistician, CDRH/OSB/DBS/GSDB, FDA; Francis Ruvuna, Director, Biostatistics and Clinical Informatics, Cyberonics

Speakers: Ted Kaptchuk, Professor of Medicine, Harvard Medical School, Martin Fahy, Principal Biostatistician, Medtronic, Inc., Zhiwei Zhang, Ph.D., Math Statistician, Division of Biostatistics, FDA

Knowledge of types and of the mechanisms of placebo effect and the influence on the results of different effectiveness endpoints in device clinical studies are receiving great attention. Placebo effect may obscure or enhance the strength of expression of treatment interventions under study. This session will provide insights for various components of placebo effect in terms of magnitude, duration, clinical implications, underlying patterns of placebo response and potential study designs and statistical analyses to minimize their effect. An overview of recent research on placebo effect will be followed by two case studies illustrating lessons learned from both industry and FDA perspectives.

10:30 – 10:45 BREAK
10:45 – 12:15  Adaptive Design – Case Studies

**Co-organizers:** Jack Zhou, Mathematical Statistician, CDRH, FDA; Terry Liao, Manager, Biostatistics, (BSCI)

**Speakers:** Hong (Laura) Lu, Ph.D., Mathematical Statistician, Division of Biostatistics, FDA CDRH, Christopher Coffey, Ph.D., Professor of Biostatistics, The University of Iowa, College of Public Health, Joseph (Joe) Massaro, Ph.D., Professor of Biostatistics Boston University School of Public Health, Statistical Consultant, Harvard Clinical Research Institute

In recent years, adaptive designs are receiving a lot of attention in the medical device and clinical trials community. One of the most attractive features of adaptive designs is the ability to adjust the sample size during an interim analysis - sometimes called the sample size re-estimation (SSR). Although there are many statistical methods that address SSR theoretically, the practical issues (e.g. logistics) and regulatory aspect of SSR are frequently hot topics for debate. We invite speakers from FDA, industry and academia to go through case studies where SSR were used and what were the lessons learned from the case studies.

12:15 – 1:15  LUNCH

1:15 – 2:45  Frequently Encountered Study Design Considerations

**Co-organizers:** Chul Ahn, Team Leader, FDA; Zengri Wang, Director, Biostatistics, Covidien

**Speakers:** Vandana Mukhi, PhD, Mathematical Statistician, CDRH/FDA; Daniel Cher, MD, President, Wild Iris Consulting; Zengri Wang, PhD, Director, Biostatistics, Covidien

This session will cover study design considerations frequently encountered in the planning stages of clinical trials. It will include minimizing bias, repeated measures, multi-regional design, predefined adaptation, sample sizes for subgroups, risk/benefit evaluation and superiority claim in a non-inferiority trial among others.

2:45 – 3:00  BREAK

3:00 – 4:30  Missing Data in a Composite Endpoint

**Co-organizers:** Vandana Mukhi, Mathematical Statistician, CDRH/OSB/DBS, FDA; Roseann White, Director, Global Biometrics, Abbott Vascular

**Speakers:** Dr, Hui Quan, Senior Director, Sanofi; Dr, Yunling Xu, Branch Chief, FDA/CDRH; Roseann White, Director, Global Biometrics, Abbott Vascular

Composite endpoints are often used in medical device trials. A question arises when missing data occurs in the components of the composite endpoint. In this session speakers will provide examples of when such data may arise, discuss potential problems and provide approaches for the analysis of composite endpoints with missing data in components.
When the marketed version of a Companion Diagnostic test (CDx) is not available for use during the pivotal drug trial, a bridging study may be conducted to determine the effectiveness of the final CDx for its intended use by re-analyzing representative samples from the drug trial using the final CDx. On the other hand, when therapeutic efficacy for a follow-on CDx cannot be directly assessed using representative samples from the drug trial of the approved CDx, an external study may be conducted to assess the concordance between the follow-on CDx and the approved CDx with the same therapeutic indication. Challenges arise when trying to extrapolate results from these types of studies and linking these results to patient level clinical data as from the original clinical trial. This session aims to understand these challenges and explore the regulatory pathways for gaining approval for a companion diagnostic device by way of bridging and follow-on studies.

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streamlined and efficient review process. Guidance for the estimates of clinical margins, equivalence and non-inferiority tests, and choice of assessment metrics will be presented. These challenges as well as the expectations from customers will be discussed.

2:45 – 3:00  BREAK

3:00 – 4:30  Diagnostic Monitoring Studies

Co-organizers: Bipasa Biswas, Statistician, OSB-DBS/CDRH, FDA; Susan Gawel, Statistical Project Manager, Abbott Diagnostics

Speakers: Dr. Zhiheng Xu, Statistical Reviewer, Diagnostic Devices Branch, CDRH/FDA; Zoe Welsh, Principal Statistician, Research and Development, Abbott Diabetes Care; Dr. Danping Liu, Investigator, Biostatistics and Bioinformatics Branch, NIH/NICHD

Various diagnostic devices can be used for monitoring in a temporal sequence as well as to detect events over time. Examples of such monitoring devices include blood pressure monitors, continuous glucose monitors, and scalp EEG recordings for detecting seizures etc. This session will discuss considerations in the study design and analysis of diagnostic monitoring studies, such as the use of reference or non-reference standards, diagnostic performances and the correlation due to multiple events per person.