DIA

DIA/FDA Biostatistics Industry and Regulator Forum

Virtual Event: April 14-16

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Overview

The *DIA/FDA Biostatistics Industry and Regulator Forum* is a unique forum addressing the statistical issues associated with the development and review of therapeutic drugs, biologics, devices, combination, and other medical products. As an open forum to discuss timely topics of mutual theoretical and practical interest to statisticians and clinical trialists, this meeting focuses on the regulatory and statistical challenges associated with innovative approaches to the design and analysis of clinical trials data and measuring the progress with the implementation of innovative solutions.

An important purpose of the forum is to advance the dialogue between industry, regulatory agencies, and academia around policy, regulation, development, and review of medical products in the context of today's scientific and regulatory environments. The program is developed collaboratively by FDA, industry, and academic experts who team up to ensure that each session brings all stakeholder perspectives to the discussion.

Attend the DIA/FDA 2021 Biostatistics Industry and Regulator Forum and join leading edge discussions: statistical analyses in COVID-19 interrupted trials and therapeutic/vaccine trials, RWE and its use in regulatory decision making pre-marketing, approaches to the incorporation of external controls – applicability and methods, the FDA RCT DUPLICATE project, enhancing diversity in clinical trial populations, and so much more!

Who Should Attend

Professionals from industry, academia, and government involved in all phases of the medical product lifecycle who are interested in the application of statistics to advance biopharmaceutical development and accessibility including:

- Biotechnology
- Clinical Data Management/eClinical
- Comparative Effectiveness/Health Technology Assessment
- Clinical Safety/Pharmacovigilance
- Clinical Research
- eClinical
- Pharmacology
- Quality Assurance, Control
- Regulatory Affairs
- Research & Development
- Study Endpoints/Clinical Outcomes Assessments
- Statistics

Highlights

What is happening at *DIA/FDA Biostatistics Industry and Regulator Forum*:

- In-depth discussions on new, revised, and anticipated guidances and emerging policy issues
- Senior Leaders Town Hall: An open discussion lead by an expert panel of leaders from industry and regulatory agencies
- Each session is co-chaired by an Industry-FDA team
- DIA Statistics and Data Science Open Community Meeting

Schedule At-A-Glance

SHORT COURSE | MONDAY, APRIL 12

12:00-4:00PM	**Short Course 1:** Designing, Integrating, and Analyzing RCT/RWE in Safety Decision Making

SHORT COURSE | TUESDAY, APRIL 13

10:00AM-2:00PM	**Short Course 2:** Statistical Analyses Targeting Estimands

DAY ONE | WEDNESDAY, APRIL 14

10:00-10:15AM	**Welcome and Opening Remarks**
10:15-10:45AM	**Keynote Address:** The Development and Deployment of COVID-19 Vaccines
10:45-11:00AM	Break
11:00AM-12:30PM	**Session 1:** COVID-19 Treatments and Vaccines: Statistical Challenges and Lessons Learned
12:30-1:30PM	Break
1:30-3:00PM	**Session 2:** Impact of COVID-19 on Clinical Trials
3:00-3:15PM	Break
3:15-4:45PM	**Session 3:** Master Protocols in the COVID-19 Pandemic and Beyond

DAY TWO | THURSDAY, APRIL 15

10:00-11:30AM	**Session 4:** Use of Real-World Evidence for Pre-Marketing Regulatory Decision Making: Current and Future
11:30-11:45AM	Break
11:45AM-1:15PM	**Session 5:** New Uses of External Controls Leveraging Patient Level Data and Statistical Matching or Weighting in a Regulatory Setting
1:15-2:15PM	Break
2:15-3:15PM	Community Discussion of Data Science in Relation to Drug Development
3:15-3:30PM	Break
3:30-5:00PM	**Session 6:** Diversity and Inclusion

DAY THREE | FRIDAY, APRIL 16

10:00-11:30AM	**Senior Leaders Town Hall**
11:30-12:00PM	Break
12:00-1:30PM	**Session 7:** Communicating and Estimating the Estimand: The Impact of the Estimand Framework
1:30-2:30PM	Break
2:30-3:30PM	**Session 8:** Current Issues in Adaptive Design and Evolving ICH E20 Guidance
3:30-3:45PM	Closing Remarks

Learning Objectives

At the conclusion of this forum, participants should be able to:

- Describe the challenges and opportunities in applying external control data to clinical development
- Explain the use of RWE to support regulatory submissions
- Apply the FDA guidance to enhance diversity and inclusion in clinical trials
- Apply lessons learned from the COVID-19 pandemic to enhance statistical leadership, collaboration, and study design in drug development
- Identify the operational challenges and considerations in executing Master Protocol
- Describe the most common designs using Master Protocols and their utility in solving clinical development challenges during the COVID-19 pandemic
- Evaluate the differences among stakeholder views on clinically meaningful estimands
- Apply the estimand framework to the learner's own clinical investigations
- Describe the collaboration of statistical science with data science in drug development

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SHORT COURSE | MONDAY, APRIL 12

12:00-4:00PM

Short Course 1: Designing, Integrating, and Analyzing RCT/RWE in Safety Decision Making

Session Chair
Rima Izem, PhD, Associate Director, Statistical Methods and Consulting, Novartis

Instructors
Yong Ma, PhD, Lead Mathematical Statistician, Office of Biostatistics, CDER, FDA

Richard Zink, PhD, Vice President, Data Management, Biostatistics and Statistical Programming, Lexitas Pharma Services

James Buchanan, PharmD, President, Covilance LLC

William Wang, PhD, President, Merck & Co, Inc.

In recent years, we have seen increasing interest in real world evidence for regulatory decision making (eg FDA RWE framework, ICH E8 R1) while promoting clearly defined scientific questions and causal assessment (eg ICH E9 R1). These interests are particularly tangible in aggregated safety evaluation from randomized clinical trials (RCTs) and real-world evidence (RWE). In this short course, we will review the evolving landscape and describe key components of safety signaling and causal assessment. We will summarize design considerations for pragmatic and observational trials for safety evaluation and highlight safety analytical approaches with illustrative examples.

At the conclusion of this short course, participants should be able to:

- Discuss the evolving landscape in safety evaluation with randomized and observational evidence
- Identify the key signal management components and key safety considerations for RCT/RWE
- Apply analytical methods for observational and randomized data sources

SHORT COURSE | TUESDAY, APRIL 13

10:00AM-2:00PM

Short Course 2: Statistical Analyses Targeting Estimands

Session Chair
Brenda Crowe, PhD, Senior Research Advisor, Global Statistical Sciences, Eli Lilly and Company

Instructors
Heinz Schmidli, PhD, MSc, Executive Director, Statistical Methodology, Novartis Pharma AG, Switzerland

Frank Bretz, PhD, Distinguished Quantitative Research Scientist, Statistical Methodology, Novartis Pharma AG, Switzerland

Björn Bornkamp, PhD, MSc, Senior Director, Statistical Methodology, Novartis Pharma AG, Switzerland

Dong Xi, PhD, Associate Director, Statistical Methodology, Novartis Pharmaceuticals

The recent release of the ICH E9 addendum on estimands has a profound impact on clinical trial analysis. Health authorities require that methods for analyses and sensitivity analyses target the estimand of interest. This course discusses how to identify and implement analyses approaches as well as sensitivity analyses that are aligned with the estimand. We will illustrate this with case studies on clinical trials with various endpoints (continuous, binary, time-to-event, recurrent events).

At the conclusion of this short course, participants should be able to:

- Identify an appropriate primary analysis method that targets the estimand of interest, fully aligned with the ICH E9 addendum
- Discuss strategies to change assumptions made for the primary analysis in sensitivity analyses
- Implement appropriate analyses and sensitivity analyses

DAY ONE | WEDNESDAY, APRIL 14

10:00-10:15AM

Welcome and Opening Remarks

10:15-10:45AM

Keynote Address: The Development and Deployment of COVID-19 Vaccines

Session Chair
Brenda Crowe, PhD, Senior Research Advisor, Global Statistical Sciences , Eli Lilly and Company

Vaccine development was greatly accelerated during the COVID-19 pandemic and has resulted in the authorization of several different COVID-19 vaccines globally. This acceleration was achieved without sacrificing the quality, safety, or efficacy of the development process. Understanding the methods used to achieve this is informative. Additionally, the availability of extensive post-authorization safety surveillance networks and methodologies helped achieve this accomplishment.

Speaker
Peter Marks, MD, PhD, Director, Center for Biologics Evaluation and Research

10:45-11:00AM

Break

11:00AM-12:30PM

Session 1: COVID-19 Treatments and Vaccines: Statistical Challenges and Lessons Learned

Session Co-Chairs
Brenda Crowe, PhD, Senior Research Advisor, Global Statistical Sciences, Eli Lilly and Company

Shiowjen Lee, PhD, Deputy Director, Division of Biostatistics, OBE, CBER, FDA

The COVID-19 pandemic brought many challenges to sponsors and regulatory bodies wishing to develop vaccines and/or treatments for COVID-19. It was imperative to work at top speed and the standard of care was changing rapidly. The FDA has issued Emergency Use Authorization (EUA) for both vaccines and treatments. This session will include case studies that highlight particular issues of COVID-19 clinical development and how they were dealt with by sponsors and the FDA. Speakers will discuss the statistical issues and solutions to handle the unprecedented uncertainty and changing dynamics.

Designing and Analyzing Studies During an Evolving Pandemic: What Can we Learn for the Future?
Ian Hirsch, PhD, Respiratory/Infection Biologics and Vaccine Products Biometrics Strategy Lead, AstraZeneca

Regulatory Review of EUA and Statistical Issues
Tsai-Lien Lin, PhD, Branch Chief, Vaccine Evaluation Branch, Division of Biostatistics, CBER, FDA

Building a Plane While Flying It: Reflections on Repurposing a Drug to Treat COVID-19
Yanping Wang, PhD, Senior Director-Statistics, Eli Lilly and Company

12:30-1:30PM — **Break**

1:30-3:00PM — **Session 2:** Impact of COVID-19 on Clinical Trials

Session Co-Chairs
Lisa Renee Bailey Iacona, PhD, MPH, Vice President, Oncology & Immuno-Oncology, AstraZeneca Pharmaceuticals LP

Fairouz Makhlouf, PhD, Mathematical Statisticain, CDER, FDA

The COVID-19 pandemic may have affected the ability for patients and physicians to follow standard of care procedures and visits. Medical care saw increased use of home health/telemedicine and greater potential for missed in-person visits and tests. This session will highlight how this impact on clinical trials has been assessed through the use of modelling and simulation, case studies and regulatory guidance.

Addressing the Impact of the COVID-19 Pandemic on Survival Outcomes in Randomized Phase III Oncology Trials
Binbing Yu, Statistical Science Director, Head of Statistical Innovation, AstraZeneca Pharmaceuticals LP

An Enterprise Approach to Handle the Impact of COVID-19 Pandemic on Clinical Trials
Yihua Gu, MS, Senior Director of Statistics, Immunology TA Head, Abbvie

Speaker
Martin Klein, Mathematical Statistician, CDER, FDA

3:00-3:15PM — **Break**

3:15-4:45PM — **Session 3:** Master Protocols in the COVID-19 Pandemic and Beyond

Session Co-Chairs
Rebecca Hager, PhD, Mathematical Statistician, OTS, CDER, FDA

Cindy Lu, PhD, Director Biostatistics, Biogen

Venkat Sethuraman, PhD, Senior Vice President, Biometrics and Data Sciences, Bristol Myers Squibb

This session will review current design and implementation considerations, practical challenges, regulatory landscape, and perspectives from a patient advocate group on master protocols. The considerations covered in this session applies to various therapeutic areas, though specific considerations will also be presented for COVID-19 master protocols

Master Protocols: Benefits for Clinical Trial Participants and Patients
Robert Beckman, MD, Professor of Oncology, Bioinformatics, and Biomathematics, Georgetown University Medical Center

Speakers
Martin Posch, PhD, Professor, Medical University of Vienna, Austria

Gregory Levin, PhD, Deputy Director, Division of Biometrics III, Office of Biostatistics, OTS, CDER, FDA

DAY TWO | THURSDAY, APRIL 15

10:00-11:30AM — **Session 4:** Use of Real-World Evidence for Pre-Marketing Regulatory Decision Making: Current and Future

Session Co-Chairs
Judith Maro, PhD, MS, Assistant Professor, Department of Population Medicine Harvard Pilgrim Health Care Institute

Yuan-Li Shen, DrPH, Acting Deputy Division Director, Division of Biometrics V, Office of Biostatistics, OTS, CDER, FDA

Ram Tiwari, PhD, Head of Statistical Methodology, Bristol Myers Squibb

Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions in recent years. The 21st Century Cures Act, passed in 2016, places additional focus on the use of the RWD to support regulatory decision making. The purpose of this session is to discuss the use of the RWD to support regulatory submission in a pre-marketing setting. The current progress and future prospect of using RWE, approaches/methods to optimize the utility of RWE, and examples of using RWD to support a submission will be discussed. The applicability and limitation of using RWE will also be examined per regulatory and industry's point of views.

Real-World Evidence Experience in Cell Therapy Submission: Lessons Learned
Lihua Yue, PhD, Associate Director, Biostatistics, Bristol Myers Squibb

FDA's Real-World Evidence Program
John Concato, MD, MS, MPH, Associate Director of Real-World Evidence Analytics, Office of Medical Policy, CDER, FDA

Key Considerations in the Use of RWE for Regulatory Decisions
Weili He, PhD, Senior Director, Head of Global Medical Affairs Statistics, DSS, AbbVie

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11:30-11:45AM — **Break**

11:45AM-1:15PM — **Session 5:** New Uses of External Controls Leveraging Patient Level Data and Statistical Matching or Weighting in a Regulatory Setting

Session Co-Chairs
Ruthie Davi, MS, PhD, Vice President, Data Science and Statistician, Acorn AI, A Medidata Company

Meiyu Shen, PhD, Expert Mathematical Statistician, Office of Translational Sciences, CDER, FDA

Increased availability of patient-level data and recent regulatory decisions encouraging the use of innovative approaches to accelerate medical product development are fueling the impetus to incorporate external control data into clinical development settings. Potential patient-level data sources are wide-ranging and include historical clinical trials data available through growing data sharing programs, registry data collected in order to advance the understanding of a particular disease, and real-world data electronically stored as part of clinical practice. This session will 1) discuss statistical methods, such as matching and weighting, that are fueling the ability to create well-balanced external control cohorts, 2) examine statistical considerations specific to the various types of patient-level data sources, and 3) present case studies and examples of the use of external controls in clinical development and regulatory settings.

Speaker
Antara Majumdar, PhD, Director of Statistics, Acorn AI by Medidata, a Dassault Systèmes company

Across-Trial Propensity Score Analysis to Support Contribution of Components of Oncology
Brent McHenry, PhD, Director, Biostatistics RCC and Prostate Lead, Global Biometric and Data Sciences, Oncology, Bristol-Myers Squibb

Panelists
Pallavi Mishra-Kalyani, PhD, Lead Mathematical Statistician, CDER, FDA

Aloka Chakravarty, PhD, Senior Statistical Advisor, Office of the Commissioner, FDA

1:15-2:15PM — **Break**

2:15-3:15PM — **Community Discussion of Data Science in Relation to Drug Development**

Session Co-Chairs
Ruthie Davi, PhD, **MS,** Vice President, Data Science and Statistician, Acorn AI, A Medidata Company

Stella Grosser, PhD, MS, Division Director, Office of Biostatistics, OTS, CDER, FDA

This will be a community discussion of data science. Several panelists with experience in the area will be available to share their knowledge.

Speaker
Nareen Katta, MBA, MS, Senior Director and Head of Clinical Analytics, Abbvie

Panelists
Paul Schuette, PhD, MA, Mathematical Statistician, OB, OTS, CDER, FDA

Matt Austin, MS, Executive Director, Data Sciences, Center for Design and Analysis, Amgen Inc.

Joan Buenconsejo, PhD, Senior Director, Biostatistics, AstraZeneca

3:15-3:30PM **Break**

3:30-5:00PM **Session 6:** Diversity and Inclusion

Session Co-Chairs
Rima Izem, PhD, Associate Director, Statistical Methods and Consulting, Novartis

Mark Rothmann, PhD, Acting Director, Division of Biometrics II, Office of Biostatistics, CDER, FDA

Recent FDA documents and action plans have provided guidance to industry on improving the diversity in clinical trials and enhancing the collection and availability of demographic subgroup data. Diversity in clinical trials can be improved by broadening eligibility criteria, avoiding unnecessary exclusions, and improving trial recruitment outreach. Having a more diverse clinical trial population will facilitate evaluation of treatment effect in different subgroups and will answer generalizability questions to the indicated population. This session will discuss the state of the art in improving diversity in clinical trials and the implications on statistical approaches and communication of results.

Patient Diversity in Clinical Research
Rear Admiral Richardae Araojo, PharmD, MS, Associate Commissioner for Minority Health and Director of the Office of Minority Health and Health Equity, FDA

Goals of Subgroup Analyses, Assessing Standards for Analysis of Differences, and Limits of Interpretation
Steve Snapinn, PhD, Independent Consultant, Seattle- Quilcene Biostatistics LLC

Subgroups and Bayes
Thomas Louis, PhD, Professor Emeritus, Johns Hopkins Bloomberg School of Public Health

Panelists
Mark Rothmann, PhD, Acting Director, Division of Biometrics II, Office of Biostatistics, OTS, CDER, FDA

Barbara Bierer, MD, Faculty director of the Multi-Regional Clinical Trials Center, Brigham and Women's Hospital

DAY THREE | FRIDAY, APRIL 16

10:00-11:30AM **Senior Leaders Town Hall**

Session Co-Chairs
Stella Grosser, PhD, MS, Division Director, Office of Biostatistics, OTS, CDER, FDA

Lisa Lupinacci, PhD, MS, Vice President, Late Development Statistics, Merck and Co., Inc.

This session will provide an opportunity for attendees to hear senior leaders' thoughts on topics relevant to today's drug development environment. There will be several topics introduced for discussion, and the senior leaders will provide comments. There will also be an opportunity for attendees to ask questions of specific panel members or the entire panel.

Panelists
Andrew Thomson, MS, **PhD,** Statistician, Methodology Taskforce, European Medicines Agency

John Scott, PhD, MA, Director, Division of Biostatistics, CBER, FDA

Sylva Collins, PhD, Director of the Office of Biostatistics, CDER, FDA

Bruce Binkowitz, PhD, MSc, Vice President, Biometrics, Shionogi

Pandurang Kulkarni, PhD, Chief Analytics Officer R&D, Vice President of Biometrics and Advanced Analytics, Eli Lilly and Co.

Sara Hughes, Senior Vice President and Head, Biostatistics, GSK

Amy Xia, PhD, Vice President, Center for Design and Analysis, Amgen

11:30-12:00PM — **Break**

12:00-1:30PM — **Session 7:** Communicating and Estimating the Estimand: The Impact of the Estimand Framework

Session Co-Chairs
Mallorie Fiero, PhD, Lead Mathematical Statistician, CDER, FDA

Lisa Hampton, PhD, Associate Director, Statistical Methodology & Consulting, Novartis Pharma AG, Switzerland

How to specify and estimate an estimand is not just a statistical question. Close collaboration and effective communication between a variety of stakeholders is essential to ensure the estimand is aligned with the clinical trial objectives, and to align the statistical analyses with the chosen estimand. The estimand thinking process can be used to structure this workflow. At each step, discussions between statisticians and non-statisticians are needed to understand the patient journey as well as the cause and impact of intercurrent events; appreciate which questions are of primary clinical interest; and identify the plausibility of assumptions needed for a statistical analysis. In this session, through discussion and case-studies, we will explore strategies for communicating the estimand framework with clinicians and see examples of how to align the estimator with the estimand.

Speakers
Shanti Gomatam, PhD, Mathematical Statistician, CDER, Office of Biostatistics, FDA

Journey from Estimand to Estimator
Elena Polverejan, PhD, Scientific Director, Statistical Modeling and Methodology, Janssen Pharmaceuticals

Communicating and Aligning Estimands in The ICH E9 (R1) Framework
Craig Mallinckrodt, PhD, Distinguished Biostatistician, Biogen

Communicating and Estimating the Estimand: the Impact of the Estimand Framework
Anthony Man, DrMed, FRCP, Global Clinical Development Head, Communicable Diseases, Global Drug Development, Novartis Pharmaceuticals, Switzerland

Lei Nie, PhD, Associate Division of Biometrics II, Office of Biostatistics, OTS, CDER, FDA

1:30-2:30PM — **Break**

2:30-3:30PM — **Session 8:** Current Issues in Adaptive Design and Evolving ICH E20 Guidance

Session Co-Chairs
Erik Pulkstenis, PhD, Vice President, Data and Statistical Sciences, Abbvie

Fairouz Makhlouf, PhD, Mathematical Statisticain, CDER, FDA

Adaptive designs have received significant attention over the last 15 years in the literature, regulatory guidance, and clinical trial practice as their use has increased supporting both early/mid-stage trials as well as registrational trials. The potential advantages including ethical considerations, accelerated decision making and efficient resource utilization are well known as are associated challenges like type-1 error control, estimation, and vigilance required to maintain trial integrity in the context of mid-trial data analysis and decision making. Regulatory guidance has emerged from around the world and ICH harmonization is currently ongoing. In this session, we will hear from key members of the ICH E20 working group who will orient us to the process as well as discuss a variety of issues that require careful thought in the implementation of these trials.

ICH E20 Adaptive Design Guidance Development Process and Status Update
John Zhong, PhD, Vice President, Head of Biometrics, REGENXBIO, Inc.

ICH E20 Adaptive Design Considerations and Current Issues
John Scott, PhD, MA, Director, Division of Biostatistics, OBE CBER, FDA

3:30-3:45PM — **Closing Remarks**