PROGRAMME OF THE SEVENTY-SIXTH ANNUAL DEMING CONFERENCE ON APPLIED STATISTICS

Sponsored by
Deming Conference Organization
AMERICAN STATISTICAL ASSOCIATION: Biopharmaceutical Section

Three-Day Conference, December 7 – December 9, 2020
Two Short Courses, December 10 - 11 and December 14 - 15, 2020

Virtual Conference
All Times in the Schedule are U.S. EST Time

Three Keynotes on December 7-9, 2020

Keynote 1: Precision Imaging for Precision Medicine- Biomarkers and Beyond by **Sue-Jane Wang**, FDA
Keynote 2: Harnessing the Power of Statistics: Big Challenges, Big Opportunities by **Dionne Price**, FDA
Keynote 3: New Statistical Initiatives in the FDA CDRH by **Ram Tiwari**, CDRH, FDA

Twelve Sessions of Tutorials on December 7-9, 2020 and Two Short Courses on December 10-11 and 14-15, 2020

Short Course 1. Artificial Intelligence for Drug Development, Precision Medicine and Healthcare by Professor **Mark Chang**, Boston University
Short Course 2. Working with Generalized Linear and Nonlinear Mixed Models by Professor **Walter Stroup**, The University of Nebraska-Lincoln

A $4,000 college scholarship will be awarded to an undergraduate spouse, child, stepchild, or grandchild of a registrant

The 3-day Deming Conference on Applied Statistics provides a learning experience on recent developments in statistical methodologies in biopharmaceutical applications. The 76th Annual Deming Conference will be held virtually on December 7-15, 2020. There will be two parallel half-day tutorial sessions based on recently published books for the first three days for a total of 12 tutorial sessions (December 7-9). Then the conference will continue with a 2-day short course on December 10 and 11 and another on December 14 and 15. (One could conceivably register for both short courses.) The books used for the tutorial sessions and for the short courses as well as books written by invited speakers will be sold at appreciable discounted prices. The books are not included in the tutorial sessions or short course registration. Registrants are responsible to purchase the book individually.

All registration will be done electronically online. The 3-day conference starts with keynote talks at 11:00 am. The short course also starts at 11:00 am. An email will be sent registrants on November 15th with links to participate the virtual conference.

THREE-DAY REGISTRANTS WILL RECEIVE AN ELECTRONIC COPY OF THE HANDOUTS FOR ALL SESSIONS.

RECEIPTS and a CERTIFICATE OF ATTENDANCE will be distributed electronically. Register and pay for the conference online as early as possible at www.demingconference.org. This gives you an instant email acknowledgement. Payment must be paid by a credit card. E-Mail Cancellations sent to registrar@demingconference.org will be accepted until November 16th for a separate $50 fee for both the conference and courses. Afterwards, there will be no refunds, but substitution of another registrant is permissible.

There will be no Poster Session this year.

There will be student scholar presentations. Selected scholars can attend the 3-day conference without paying a registration fee. For a student scholar application, please contact Dr. Sofia Paul, Deming Scholar Chair, at sofia.x.paul@gsk.com.

Seventy-Sixth (76th) Annual Deming Conference on Applied Statistics

Virtual Conference*

Sponsored by the Biopharmaceutical Section of the ASA and the Deming Conference Organization

Monday December 7, 2020

11 AM ⇒ 12 PM Keynote: Precision Imaging for Precision Medicine- Biomarkers and Beyond by Sue-Jane Wang, FDA
Moderator: Alfred H. Balch

Sessions: 12:00 PM ⇒ 1:20 PM tutorial / 1:20PM ⇒ 1:30PM break/ 1:30 PM ⇒ 2:50 PM tutorial / 2:50 PM ⇒ 3:30 PM break

Session A	Session B 🕮
Innovative Designs for Early Phase Dose-Finding Studies Sue-Jane Wang, FDA, and Yuan Ji University of Chicago Moderator: Alfred H. Balch	**Recent Development in Analyzing Microbiome Data from Clinical Trials** Yinglin Xia, University of Illinois at Chicago and Din Chen, UNC-Chapel Hill Moderator: Walter R. Young

Sessions: 3:30 PM ⇒ 4:50 PM tutorial/ 4:50 PM ⇒ 5:00 PM break/ 5:00 PM ⇒6:20 PM tutorial

Session C	Session D
Randomization and Inference in Clinical Trials Diane Uschner, George Washington University Moderator: Alfred H. Balch	**Master Protocol and Its Application** Jingjing Ye, BeiGene, Cindy Lu, Biogen and Nicole Li, Merck & Co. Inc Moderator: Xiaoming Li

Tuesday December 8. 2020

11 AM ⇒ 12 AM: Keynote: Harnessing the Power of Statistics: Big Challenges, Big Opportunities by Dionne Price, FDA
Moderator: Naitee Ting

Sessions: 12:00 PM ⇒ 1:20 PM tutorial / 1:20PM ⇒ 1:30PM break/ 1:30 PM ⇒ 2:50 PM tutorial / 2:50 PM ⇒ 3:30 PM break

Session E	Session F
Causal Inference and Data Fusion Elias Bareinboim and Adele Ribeiro, Columbia University and Mohammad Adibuzzaman, Purdue University Moderator: Bill Wang	**Real World Evidence Landscape and Evolution in Drug Development** Jenny Fang and Melvin Olson, Novartis Moderator: Naitee Ting

Sessions: 3:30 PM ⇒ 4:50 PM tutorial/ 4:50 PM ⇒ 5:00 PM break/ 5:00 PM ⇒6:20 PM tutorial

Session G 🕮	Session H
Bayesian Adaptive Approaches Using Historical Data Brad Carlin, Counterpoint Statistical Consulting, LLC Moderator: Ivan S. F. Chan	**Targeted Estimation of Direct and Indirect Causal Effects in Clinical Trials** Jie Chen, Fang Liu and Yanping Liu, Merck & Co. Inc Moderator: Wenjin Wang

Wednesday December 9, 2020

11 AM ⇒ 12 AM: Keynote: New Statistical Initiatives in the FDA CDRH by Ram Tiwari, CDRH, FDA
Moderator Bill Wang

Sessions: 12:00 PM ⇒ 1:20 PM tutorial / 1:20PM ⇒ 1:30PM break/ 1:30 PM ⇒ 2:50 PM tutorial / 2:50 PM ⇒ 3:30 PM break

Session I	Session J
Likelihood Ratio Methodologies for Safety and Risk-Based Monitoring Lan Huang, Howard Yao and Ram Tiwari, CDRH, FDA Moderator: Bill Wang	**Answering Old Questions with New Tools: Application of the ICH E9 Addendum in Oncology** Kaspar Rufibach, Roche and Evgeny Degtyarev, Novartis Moderator: Kalyan Ghosh

Sessions: 3:30 PM ⇒ 4:50 PM tutorial/ 4:50 PM ⇒ 5:00 PM break/ 5:00 PM ⇒6:20 PM tutorial

Session K	Session L
Statistical Designs and Strategies for Oncology Drug Development Cong Chen, Merck & Co. Inc Moderator: Kalyan Ghosh	**Statistical Methods in the Clinical Development of Novel Cancer Immunotherapies** Bo Huang, Pfizer Moderator: Naitee Ting
Thursday & Friday December 10-11, 2020	Monday & Tuesday December 14-15, 2020

11:00 AM⇒12:30 PM Lecture/ 12:30 PM ⇒ 1:00 PM *Break*/ **1:00 PM⇒2:30 PM Lecture** /
2:30 PM⇒ 2:50 PM *Break* / **2:50 PM⇒4:20 PM Lecture** / **4:20 PM⇒4:30 PM** *Break* / **4:30 PM ⇒ 6:00 PM Lecture**

Artificial Intelligence for Drug Development, Precision Medicine and Healthcare 🕮	Working with Generalized Linear and Nonlinear Mixed Models 🕮
Professor Mark Chang, Boston University Moderator: Ivan S. F. Chan	Professor Walter Stroup, The University of Nebraska-Lincoln Moderator: Alfred H. Balch

All tutorial and short course titles, presenters and moderators from 1970 onward are on www.demingconference.org

🕮 Session is based on a recently published text that is available for a discounted price. The book used in tutorials or short courses is not included in registration. Attendees will be provided links and promotion codes to order the books themselves.

All times in the schedule refer to US EST Time

*Virtual conference information with links to participate will be sent to registrants on Nov 15th, 2020

Conference Speakers Biography

Mohammad Adibuzzaman (PhD in Computational Sciences from Marquette University, Milwaukee, Wisconsin). Dr. Adibuzzaman is the Assistant Director of Data and Computing at the Regenstrief Center for Healthcare Engineering (RCHE) located at Purdue University, Indiana. At Regenstrief, Dr Adibuzzaman leads the research infrastructure for data analysis and have established numerous institutional partnership such as the Laboratory for Computational Physiology at the MIT led by Roger Mark, and industry partnership for state of the art distributed database technology with Paradigm4, founded by Turing Award recipient MIT Computer Scientist Mike Stonebroker, and many intra university computing partnerships at the intersection of data science, computer science, and life sciences. He also is leading a new line of research at RCHE for explainable Artificial Intelligence (AI) in health sciences focusing on causal inference methods. The goal is to introduce new methods of explainable AI in clinical research. He maintains all of RCHEs data and computing assets with a vision for RCHE to become a collaborative hub at the intersection of technology and health science to improve health outcomes.

Elias Bareinboim (PhD in Computer Science from University of California at Los Angeles). Dr. Barinboim is an Associate Professor in the Department of Computer Science and Director of the Causal Artificial Intelligence Lab at Columbia University, New York. He is a recipient of the prestigious NSF Career Award. His research area is in the domain of artificial intelligence, more specifically in causal inference. Building on the modern language of causation emerged in the last decades, his work develops a theoretical framework for understanding, representing, and algorithmizing causal generalizations from a heterogeneous mixture of observational and experimental studies.

Brad Carlin (PhD in Statistics from University of Connecticut). Dr. Carlin is a statistical researcher, methodologist, consultant, and instructor. He spent 27 years on the faculty of the Division of Biostatistics at the University of Minnesota School of Public Health, serving as division head for 7 of those years. He has published more than 185 papers in refereed books and journals, and has co-authored three popular textbooks. From 2006-2009 he served as editor-in-chief of *Bayesian Analysis*, the official journal of the International Society for Bayesian Analysis (ISBA). During his academic career, he served as primary dissertation adviser for 20 PhD students.

Cong Chen (PhD in Statistics from from Iowa State University). Dr. Cong Chen is Executive Director of Early Oncology Development Statistics at Merck & Co., Inc. As head of the group, he oversees the statistical support of oncology early clinical development and translational biomarker research at Merck. He is a Fellow of American Statistical Association, an Associate Editor of Statistics in Biopharmaceutical Research, a member of Cancer Clinical Research Editorial Board and a co-leader of the DIA Small Population Work Stream. He has published over 75 papers and 10 book chapters on design and analysis of clinical trials, has given multiple short courses on design and analyses of clinical trials and was twice invited to give an oral presentation at the AACR Annual Meeting in recent years on design strategies for oncology drug development.

Din Chen (PhD in Statistics from University of Guelph) is the Wallace H. Kuralt distinguished professor in Biostatistics at University of North Carolina-Chapel Hill. Dr. Chen is an elected fellow of American Statistical Association (ASA), an elected member of the International Statistics Institute (ISI) and a senior expert consultant for biopharmaceuticals and government agencies with extensive expertise in clinical trial biostatistics. Dr. Chen has more than 200 referred professional publications and co-authored/co-edited 25 books on biostatistics clinical trials, biopharmaceutical statistics, interval-censored survival data analysis, meta-analysis, public health statistics, statistical causal inferences; statistical methods in big-data sciences and Monte-Carlo simulation based statistical modeling. Dr. Chen is a committee member of the Deming Conference and has been invited to give various tutorials at Deming Conference since 2011.

Jie Chen (MD from Shanghai First College of Medicine, an MPH in biostatistics & epidemiology from the University of Oklahoma Health Science Center and a PhD in statistics from Temple University). Dr. Chen is a Distinguished Scientist in Methodology Research at Merck Research Laboratories. Jie's experience includes statistical methodology research and applications in non-clinical and pre-clinical research, clinical development, and post-licensure product life-cycle management. He has given short courses at FDA/Industry statistics workshop, EMA statistics symposium and many invited talks at academic institutions and statistical conferences.

Evgeny Degtyarev (Master's in mathematics and Economics from the University of Magdeburg, Germany). Dr. Degtyarev is Global Program Biostatistics Head leading a team of quantitative scientists on CAR-T program in hematology at Novartis. Since joining Novartis in Basel in 2013, he has supported several oncology programs with targeted and immunotherapies in different stages of development. He has co-founded and co-leads the industry working group "Estimands in oncology" in Feb 2018 which has been later granted the status of EFSPI/PSI Special Interest Group and ASA Biopharmaceutical Section Scientific Working Group (www.oncoestimand.org).

Jenny Fang (MD from Xian JiaoTong University, MS in biostatistics from University of Illinois at Chicago and Health Economics and Outcomes Research from University of Washington). Jenny is a Senior Real-World Evidence (RWE) Scientist at Novartis Pharmaceuticals Corporation. During her 20+ year professional career, she spent over 3 years as a practice physician with the specialty in neuroscience and 17 years in pharmaceutical industry. Jenny held various industry positions with expanded and increased responsibilities in clinical statistics, medical affairs and real-world evidence. Her experiences cross drug development to post-approval and lifecycle management. In her current role at Novartis, she has been supporting evidence generation leveraging real-world data. She has over 20 peer-reviewed publications.

Bo Huang (PhD in Statistics from the University of Wisconsin-Madison). Dr. Huang is currently Senior Director, Head of Immuno-Oncology Statistics at Pfizer. Dr. Huang has extensive experience in the pharmaceutical industry and has significantly contributed to all aspects related to major filings to Health Authorities and approval. He is the recipient of the Craig Saxton Clinical Excellence Award at Pfizer in 2019. Dr. Huang is the author of more than 70 publications, with over 50 papers and book chapters, and over 20 abstracts. In addition, he has been serving as Guest Editor, Associate Editor and reviewer for scientific journals, serving as chair or member on professional committees of statistical associations, and was an elected Board Director of the International Chinese Statistical Association (2016-2019).

Lan Huang (Ph.D. in Statistics from University of Connecticut). From 2004 to 2009, Dr. Huang worked on cancer surveillance at national cancer institute (NCI). Dr. Huang joined FDA/CDER in 2009 as a statistical reviewer and moved to FDA/CDRH in 2016. She has reviewed submissions for both therapeutic and diagnostic products/devices and has participated in regulatory research for methodologies to improve the quality of review in statistical analysis in clinical trials and safety surveillance in CDER and CDRH.

Yuan Ji (PhD in Statistics from University of Wisconsin-Madison). Dr. Yuan Ji is Professor of Biostatistics at The University of Chicago. He is an NIH-funded PI focusing on innovative computational and statistical methods for translational cancer research. Dr. Ji is author of over 140 publications in peer-reviewed journals, conference papers, book chapters, and abstracts, including Nature, Nature Methods, JCO, JNCI, JASA, and Biometrics, across medical and statistical journals. He is the inventor of many innovative Bayesian adaptive designs such as the mTPI and i3+3 designs, which have been widely applied in dose-finding clinical trials worldwide, including trials published on Lancet Oncology, JAMA oncology and JCO. In particular, he led a publication in Nature Methods and invention of a tool called TCGA-Assembler which has been downloaded over 10,000 times worldwide. His recent work on precision medicine was elected as one of the top 10 ideas of the Precision Trials Challenge hosted by The Harvard Business School in 2015. He is also a co-founder of Laiya Consulting, Inc., focusing on innovative and adaptive designs for clinical trials in new drug development, including the development of novel early-phase statistical platform allowing seamless and efficient clinical trials with master protocols. He is an elected fellow of the American Statistical Association.

Nicole (Xiaoyun) Li (PhD in Statistics from Florida State University) Dr. Li has been working as a statistician on oncology clinical trials at Merck. She was the lead statistician for Keytruda's first regulatory submission and approval for advanced melanoma in the United States, Europe, and the rest of the world, and a key contributor to Keytruda's Prix Galien USA 2015 Award for Best Biotechnology Product. She has published more than 10 peer-reviewed articles in statistical methodologies. She is currently the president of the American Statistical Association (ASA) San Diego Chapter, to promote innovative statistical methodologies, statistical knowledge sharing, and strengthening of the local statistical community.

Fang Liu (PhD in Statistics from Temple University). Dr. Liu is a principal scientist at Merck Research Laboratories, Merck & Co., Inc. Dr Liu has been providing statistical support in various areas including early oncology studies, clinical pharmacology studies, PK-PD modeling and oncology biomarker statistics. She has been actively involved in statistical research and has authored/co-authored multiple scientific publications in peer-reviewed statistical and clinical journals. Her current research interests include causal inference, mediation analysis, basket trial design, umbrella trial design, missing data imputation, etc.

Yanping Liu (PhD in Statistics from Temple University). Dr. Liu is an Associated Principal scientist at Merck Research Laboratories, Merck & Co., Inc. She works on late stage Cardiovascular and Oncology studies. Her research interests include multiple testing, survival analysis, causal inference and mediation analysis.

Chengxing (Cindy) Lu (PhD in Biostatistics from Emory University). Dr. Lu is a director of Biostatistics in Biogen Inc, Cambridge, MA. She has been leading statistical aspects of multiple compounds in various disease areas, from early to late phases of clinical development to post-marking activities, resulting several successful regulatory approvals. Dr. Lu is currently the co-lead of master protocol design sub-team of ASA Biopharmaceutical Section Oncology Scientific Working Group. Her research interest is study designs in clinical trials, real-world evidence and designs, and oncology/rare disease drug development strategy.

Melvin Olson (PhD in Biostatistics from Harvard University). Dr. Olson is the Global Head of Real-World Data Strategy and Innovation at Novartis (Basel, Switzerland). In Olson's current role, he is responsible for promoting best practice in research methodology and applications of real-world data across all therapeutic areas to drive better decision making. Olson has a background in health economics and outcomes research;

he previously led the use of real-world evidence to transform the generation of patient insights and value for money assessments. Olson has worked in the pharmaceutical industry for over 25 years as a clinical statistician, health economics and outcomes research director, and real-world evidence expert.

Dionne Price (PhD in Biostatistics from Emory University). Dr. Price is the Director of Division of Biometrics IV in the Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration (FDA). In this role, Dr. Price provides leadership to statisticians involved in the development and application of methodology used in the regulation of drug products in therapeutic areas including anti-infectives, anti-virals, ophthalmology, rare diseases, and urology, obstetrics, and gynecology. Dr. Price is a member of the Senior Leadership Team and Statistical Policy Council within the Office of Biostatistics. She currently leads cross-cutting, collaborative efforts across FDA to advance and facilitate the use of complex innovative trial designs in pharmaceutical drug development. Dr. Price is an active member of the International Biometric Society (IBS), the American Statistical Association (ASA), and the Food and Drug Administration Statistical Association. She has served as Chair of the Biopharmaceutical Section of the ASA. Dr. Price was named a Fellow of the ASA in 2018 and is a Vice-President of the ASA.

Adèle H. Ribeiro (PhD in Computer Science from the Institute of Mathematics and Statistics of the University of São Paulo (USP), Brazil). Dr. Ribero is a Postdoctoral Researcher in the Causal Artificial Intelligence Lab at Columbia University. Her research focuses on developing the emergent field of Causal Health Sciences. She also undertook a doctoral research internship in the Developmental Neuromechanics and Communication Lab at Princeton University. Previously, she worked as a Postdoctoral Fellow in the Laboratory of Genetics and Molecular Cardiology at the Heart Institute in USP.

Kaspar Rufibach (PhD in Mathematics from University of Bern, Switzerland and Institute of Mathematical Statistics, Georg-August-University, G¨ottingen, Germany). Dr. Rufibach is an Expert Statistical Scientist in Roche's Methods, Collaboration, and Outreach group and located in Basel. He does methodological research, provides consulting to Roche statisticians and broader project teams, gives biostatistics trainings for statisticians and non-statisticians in- and externally, mentors students, and interacts with external partners in industry, regulatory agencies, and the academic community in various working groups and collaborations. He has co-founded and co-leads the European special interest group "Estimands in oncology". Kaspar's research interests are methods to optimize study designs, advanced survival analysis, probability of success, estimands and causal inference, estimation of treatment effects in subgroups, and general nonparametric statistics.

Ram C. Tiwari (Ph.D. in Mathematical Statistics from Florida State University). Dr. Tiwari is the Director for Division of Biostatistics, CDRH, effective June 27, 2016. He joined FDA in April 2008 as Associate Director for Statistical Science and Policy in the Immediate Office, Office of Biostatistics, Office of Translational Sciences, CDER. Prior to joining FDA, he served as Program Director and Mathematical Statistician in the Division of Cancer Control and Population Sciences at National Cancer Institute, NIH; and as Professor and Chair, Department of Mathematics, University of North Carolina at Charlotte. He is a Fellow of the *American Statistical Association* and a past President of the *International Indian Statistical Association*. He has published 200+ research papers on a wide range of statistical topics. His current research interests include developing frequentist and Bayesian methods in clinical trials and pre-and-post market drug/device safety evaluation.

Diane Uschner (PhD in Biostatistics from the RWTH Aachen University, Germany). Dr. Uschner is an Assistant Research Professor in the Department of Biostatistics and Bioinformatics at the George Washington University School of Public Health. Her research interests are focused on the design of clinical trials, randomization, control of bias, as well as survival analysis, penalized regression, and statistical learning. Dr. Uschner has recently developed an interest in antibacterial resistance and infectious diseases, and is serving as a biostatistician in the Antibiotic Resistance Leadership Group (ARLG). She is the PI of the Data Coordinating Center of the North Carolina COVID-19 Community Research Partnership. Dr. Uschner regularly serves as a reviewer for scientific journals, NIH grant reviews, and meeting abstracts.

Sue-Jane Wang (PhD in Statistics from University of Southern California). Dr. Wang is Associate Director for Adaptive Design and Pharmacogenomics and the Biostatistics Leader for the Biomarker Qualification Program from Office of Biostatistics, Office of Translational Sciences in Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Other than her current role representing the Office providing services to all 18 medical divisions in CDER/FDA on adaptive designed clinical trials, biomarker associated pharmacogenomics clinical trials and biomarker qualification. Dr. Wang has published over 80 peer-reviewed collaborative research papers in clinical trials, medical genetics, bioinformatics and pharmacogenomics journals and has given more than 200 invited presentations domestic and internationally. Recently, she received Thomas Teal Award for Excellence in Publishing awarded by Drug Information Association and was recognized by the statistical profession and elected a fellow in the American Statistical Association. She has served as an Editor-in-Chief for Pharmaceutical Statistics. She is an elected member of International Statistics Institute, an associate editor for Statistics in Medicine and for Statistical Biosciences Journal.

Yinglin Xia (PhD in Biostatitics from University of Illinois at Chicago). Dr. Xia is a Research Associate Professor at the Department of Medicine, the University of Illinois at Chicago, USA. Dr. Xia has worked on a variety of research projects and clinical trials in microbiome, gastroenterology, oncology, immunology, psychiatry, sleep, neuroscience, HIV, mental health, public health, social and behavioral sciences, as well as nursing caregiver. He has published more than 100 papers in peer-reviewed journals on Statistical Methodology, Clinical Trial, Medical Statistics, Biomedical Sciences, and Social and Behavioral sciences. He serves the editorial board for several scientific journals.

Zhihao Yao (Master's degree from University of Rochester). Mr. Yao has over 10-year experience of data analysis and software development. Before Mr. Yao joined FDA as a mathematical statistician in 2016, he worked as a database programmer at department of Biostatistics University of Mississippi Medical Center and a data analyst at NIH. His works are focused on software development, data analysis and data visualization.

Jingjing Ye (PhD in Statisticis from University of California, Davis). Dr. Ye currently is head of system and standard within Global Statistics and Data Sciences (GSDS) in BeiGene. She leads a team to promote statistical innovations in clinical trials, develop visualization tools to support pre-clinical and clinical development and establish standard and process within BeiGene. Before BeiGene, she was most recently a statistics team leader in the Office of Biostatistics in CDER. At CDER, she supervised a team of statistical analysts and reviewers for designing, reviewing and analyzing clinical trials to support drug approvals throughout preIND, IND, NDA/BLA and post-approval studies in oncology and hematology. She was statistical representative within the Oncology Center of Excellence (OCE) Pediatric Review sub-committee, responsible for overseeing all pediatric review operations within the OCE.

Program Committee and Deming Conference Officials

Monday December 7, 2020 12:00 PM – 2:50 PM

Session A

Innovative Designs for Early Phase Dose-Finding Studies

Sue-Jane Wang, FDA, and Yuan Ji University of Chicago

Moderator: Alfred H. Balch

The goal of a first-in-human clinical trial aims at exploring the safety and tolerability of an experimental treatment. Traditionally, fixed rule approaches, such as 3+3, 4+4, are commonly proposed for early phase clinical trials. Statistical literature has shown improved performance characteristics in almost all scenarios explored in the simulation studies when flexibility is built-in prospectively in a fixed rule or when model-based approaches are used. As a result, we are seeing a growing adoption of newer methodologies in early phase trial implementations.

In this tutorial, we plan for three sessions, a methodology and application session, a regulatory consideration and rationale session, and software demo session. At the conclusion of the short course, the participants will learn and apply dose finding methods suitable for their consideration. We note that proper dose selection in early-phase clinical trials will be further experimented in later phase clinical trials aiming for successful pharmaceutical development.

Outline:

- Opening and Overview
- Methodologies and Applications
  - Phase 1a dose escalation
  - Phase 1b cohort expansion
  - Drug combination dose finding
  - Immune oncology dose finding with delayed outcomes
  - Designs and methods for basket screening trials
- Regulatory considerations and rationales
  - Brief Overviews on Regulatory Guidance for Early Phase Dose Finding, Cohort Expansion, Adaptive Design, Master Protocol, New Drug Combinations
  - Some recent case studies utilizing innovative design strategies in early-phase dose finding studies
- Software demo with Q&A

Session B

Recent Development in Analyzing Microbiome Data from Clinical Trials

Yinglin Xia, University of Illinois at Chicago and Din Chen, UNC-Chapel Hill

Moderator: Walter R. Young

This tutorial provides a thorough presentation of biostatistical analyses of microbiome data with detailed step-by-step illustrations on their implementation using R. Examples of microbiome clinical trial data are based on the authors' microbiome studies and publicly available datasets in human therapeutic areas such as anti–programmed cell death 1 protein (PD-1) immunotherapy in melanoma cancer patients, anti-TNF in IBD patients. After understanding the application, various biostatistical methods appropriate for analyzing data from microbiome clinical trials are identified. Then statistical programming code is developed using appropriate R packages to analyze the data. The code development and results are presented in a stepwise fashion. This stepwise approach should enable attendees to follow the logic and gain an understanding of the analysis methods and the R implementation so that they may use R to analyze their own microbiome data.

Topics To Be Covered: Overview the next-generation sequencing techniques: 16S rRNA and Shotgun metagenomics approaches.

1. Illustrate the microbiome clinical trial data structure and features using our microbiome studies and real trials using anti–programmed cell death 1 protein (PD-1) immunotherapy in melanoma cancer patients, anti-TNF in IBD patients, and describe the challenges of analyzing microbiome data.
2. Exploratory analysis of microbiome data. We will illustrate several most widely used ordination techniques in microbiome studies, such as principal components analysis (PCA), principal coordinate analysis (PCoA), constrained correspondence analysis (CCA).
3. Univariate and multivariate community analyses. We will cover some standard statistical methods such as Kruskal-Wallis test and specially designed methods for microbial ecology such as Permutational MANOVA, analysis of similarity (ANOSIM).
4. Compositional analysis of microbiome data. We will start to introduce why microbiome data are compositional and illustrate group comparisons using a compositional package ALDEx2.
5. Modeling over-dispersed microbiome data. We will illustrate analyzing microbiome data using edgeR and DESeq2 packages.
6. Modeling zero-inflated microbiome data. We will illustrate how to use standard zero-inflated and zero-hurdle models to analyze microbiome data and also describe their limitations.
7. Longitudinal microbiome data analysis. We will illustrate how to use zero-inflated beta regression model (ZIBR) to analyze longitudinal microbiome data.

Monday December 7, 2020 3:30 PM - 6:20 PM

Session C

Randomization and Inference in Clinical Trials

Diane Uschner, George Washington University

Moderator: Alfred H. Balch

Randomization in clinical trials is a design technique that tends to balance treatment groups with respect known and unknown covariates. It is therefore commonly regarded as the key component of clinical trials that provides comparability of treatment groups. Despite the favorable properties of randomization, a randomized clinical trial (RCT) can still suffer from a lack of comparability among the treatment groups. Bias may arise for example from unobserved time trends, or from predictability of treatment assignments. Comparability is of special importance in small population groups (SPG) that arise in pediatric trials and clinical trials of rare diseases. Trials in SPG are frequently conducted as multi-arm trials to achieve greater efficiency through a shared control group. An important feature of randomization that is often overlooked is that it provides a valid basis for inference. This course will be divided into two parts. First, we will cover the basics of randomization in clinical trials; goals and ethics; restricted and adaptive randomization; quantification of bias; and regulatory guidelines. The methods will be illustrated using available software packages and shiny apps. The second part of the workshop will cover randomization as a basis for inference. This section will cover statistical and practical properties including the efficient implementation and extensions to causal inference.

Session D

Master Protocol and Its Application

Jingjing Ye, BeiGene, Cindy Lu, Biogen and Nicole Li, Merck & Co. Inc

Moderator: Xiaoming Li

As the paradigm of drug development shifts to personalized medicine and targeted therapies, pool of eligible clinical trial patients becomes increasingly smaller and there is a need for rapid learning and confirmation of clinically meaningful treatment effect. Master protocol, including umbrella, basket, and platform trials, promotes innovation in clinical trials and aims at improving efficiency, avoiding duplication and competition, and accelerating the drug development process. Though master protocols used to be primarily sponsored by nonprofit organizations, academic institutes and government agencies mostly in oncology area, there is a growing trend of conducting clinical trials using master protocol in recent years from the pharmaceutical industry in oncology and other therapeutic areas. Regulatory agencies across the globe have issued guidance on master protocols. In 2018, the ASA Biopharmaceutical Section Oncology Scientific Working Group (SWG) was chartered to explore innovative statistics in oncology drug development and a sub-team on master protocol in oncology was formed. In this short course, instructors from the Oncology SWG master protocol sub-team will provide an overview on master protocol, its regulatory landscape, statistical methodologies, special statistical considerations, challenges and opportunities both statistically and operationally. The last part of this short course will include a case study of a Pediatric platform trial: NCI-COG Pediatric MATCH, with detailed illustrations on how to implement the considerations discussed in the earlier part of the short course. See below the structure of the short course:

Part 1: Overview of master protocol

a. Overview of master protocol: Definitions, Examples
b. Review of Regulatory Landscape: US and Rest-of-World regulatory guidance

Part 2: Novel statistical methodologies used in master protocol trials, statistical and operational consideration

Part 3: Case Study of Pediatric Platform Trial: NCI-COG Pediatric MATCH

Tuesday December 8, 2020 12:00 PM – 2:50 PM

Session E

Causal Inference and Data Fusion

Elias Bareinboim and Adele Ribeiro, Columbia University and Mohammad Adibuzzaman, Purdue University

Moderator: Bill Wang

Causal inference is usually dichotomized into two categories, experimental (Fisher, Cox, Cochran) and observational (Neyman, Rubin, Robins, Dawid, Pearl) which, by and large, are studied separately. Experimental and observational studies are but two extremes of a rich spectrum of research designs that generate the bulk of the data available in practical, large-scale situations. In typical medical explorations, for example, data from multiple observations and experiments are collected, coming from distinct experimental setups, different sampling conditions, and heterogeneous populations.

In this short course, we will discuss the data-fusion problem, which is concerned with piecing together multiple datasets collected under heterogeneous conditions so as to obtain valid answers to causal queries of interest. The availability of multiple heterogeneous datasets presents new opportunities to causal analysts since the knowledge that can be acquired from combined data would not be possible from any individual source alone. However, the biases that emerge in heterogeneous environments require new analytical tools. Some of these biases, including confounding, sampling selection, and cross-population biases, have been addressed in isolation, largely in restricted parametric models. We will present our general non-parametric framework for handling these biases and, ultimately, a theoretical solution to the problem of fusion in causal inference tasks.

Session F

Real World Evidence Landscape and Evolution in Drug Development

Jenny Fang and Melvin Olson, Novartis

Moderator: Naitee Ting

Real world evidence (RWE) is the evidence obtained from real world data (RWD) through real world clinical practice outside of randomized clinical trials (RCTs). It is playing an increasing role in drug development and health care decision making. It has been used to monitor postmarket safety and to make regulatory decisions by health authorities; to support coverage decisions by payers; to support clinical practice and update clinical guidance by health care community; and to support clinical trial designs and evidence generation by biotechnology and pharmaceutical manufacturers. Classical methods (e.g. propensity score matching, causal inferential analyses etc.) have been widely used in RWE generation. Health authority started to assess the RWE with FDA published the first draft guidance of Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics in May, 2019. Criticisms of RWD/RWE of lack of causal inference, inability to control confounding exist. The efforts of increasing the transparency, reproducibility and repeatability of RWE are currently ongoing. Advanced analytics approach such as machine learning & artificial intelligence also started to be applied to RWD. This session will cover landscape and evolution of RWE in drug development.

Tuesday December 8, 2020 3:30 PM - 6:20 PM

Session G 🕮

Bayesian Adaptive Approaches for Using Historical and Auxiliary Data in Drug and Medical Device Approvals

Brad Carlin, Counterpoint Statistical Consulting, LLC

Moderator: Ivan S. F. Chan

As clinical trial costs continue to rise, industry statisticians have faced increasing pressure to develop and utilize more efficient statistical techniques. Fortunately, regulators at FDA, EMA and elsewhere are increasingly comfortable with Bayesian statistical techniques, which permit formal borrowing of strength from expert opinion and auxiliary data, and yield full probabilistic inference regarding model quantities of interest. These approaches are increasingly being encouraged by FDA though its Complex Innovative Trial Design (CID) initiative, consistent with the 21st Century Cures Act, passed by the US Congress in late 2016, and PDUFA VI. Bayesian statistical methods facilitate adaptive dose-finding and randomization, and have a long history of success in early phase clinical trial settings where patients and other resources are scarce and/or where reliable external information is available. However, it's often unclear when and how much strength to borrow from external data sources, especially if they are historical, observational, or both.

In this tutorial, after a very brief review of the Bayesian approach, we illustrate its use in simple data combination methods, including traditional two-step approaches, as well as ones using power priors, commensurate priors, and robust mixture priors for incorporating sensibly downweighted versions of the auxiliary information. Here, the notion of effective sample size is important to judge the relative importance and impacts of the various data sources. Techniques specific to rare and pediatric diseases will be discussed, as will an approach for optimally selecting the timing of an interim look at the data. On the drug side, the use of PK/PD data to expand the range of useful auxiliary information will be explored. We also consider the problem of borrowing strength from observational data, where propensity score matching offers a way to correct for possible biases arising from the lack of randomization.

Throughout, we illustrate with practical examples from the instructor's own consulting practice, which has included both device and drug approvals. In particular, we begin with a colorectal cancer case study in which relying solely on historical control information erroneously identifies a significant treatment effect. We then catalog situations where borrowing historical information may or may not be advisable. We also consider a Bayesian adaptive platform design that uses commensurate prior methods at interim analyses to borrow adaptively from the control group of an earlier-starting trial, which we show compares favorably to an ad hoc frequentist "all-or-nothing" borrowing approach. Finally, we discuss computational tools available to help implement the adaptive Bayesian inference methods presented.

Carlin, B.P. and Louis, T.A. (2009). *Bayesian Methods for Data Analysis*, 3rd ed. Boca Raton, FL: Chapman and Hall/CRC Press.

Berry, S.M., Carlin, B.P., Lee, J.J., and Muller, P. (2011). *Bayesian Adaptive Methods for Clinical Trials*. Boca Raton, FL: Chapman and Hall/CRC Press.

Session H

Targeted Estimation of Direct and Indirect Causal Effects in Clinical Trials

Fang Liu, Yanping Liu and Jie Chen Merck & Co. Inc

Moderator: Wenjin Wang

Clinical trials establishing a therapeutic effect of a new drug on a clinical outcome often need to further investigate the magnitude of different pathways and mechanisms of action by which the drug produces the outcome. Such an investigation is called (causal) mediation analysis, which partitions the total drug effect into direct and indirect effects. Indirect effect represents drug effects through intermediate variables or mediators, whereas direct effects work through other mechanism. For example, canagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, is shown to reduce the risk of heart failure directly and indirectly through some post-randomization biomarkers (Li et al., 2020); physical activity may improve self-reported cognition of breast cancer survivors by decreasing anxiety (Hartman et al., 2019); a problem-solved educational program may help reduce the risk of depressive symptoms in low-income mothers primarily by reducing maternal stress (Silverstein et al., 2018; Lee et al., 2019). Causal mediation analysis helps us understand how an intervention works and enable us to predict possible outcomes under a rich variety of conditions and interventions. Traditionally, mediation analysis is conducted through two approaches that are often referred to as the "difference method" and "product method". This tutorial will first describe the mediation formula of Pearl (2012, 2014) using structural causal models and then introduce the targeted maximum likelihood framework of van der Laan and Rubin (2006) and van der Laan and Rose (2011) to construct semiparametric, multiple robust estimators for direct and indirect treatment effects. Examples are given throughout the tutorial for continuous, binary, and time-to-event outcome variables.

Key words: Clinical trials, intermediate variable, mediation analysis, mediation formula, targeted maximum likelihood estimation.

Wednesday December 9, 2020 12:00 PM – 2:50 PM

Session I

Likelihood Ratio Methodologies for Safety and Risk-Based Monitoring

Lan Huang, Howard Yao and Ram Tiwari, CDRH, FDA

Moderator: Bill Wang

With greater technological advancements and medical innovations, post-market safety surveillance plays a critical role in ensuring public health. Companies manufacturing medical products evaluate the safety issues/signals of the medical products during the product development and, also monitor the safety issues/signals after the product is on the market after approval of FDA. Consistent with the mission to protect and advance the public health, FDA also monitors the benefit-risk balance of medical products over their life cycle. A safety signal identified in the development and post-market surveillance includes information suggesting a possible safety concern that need further assessment.

In this interactive course, we will review some common Frequentist and Bayesian data mining methods for evaluation of safety signals in large post-market data including individual case reports obtained from spontaneous reporting systems (SRS), such as the FDA adverse event reporting system (FAERS). The main focus of this course is on the Likelihood Ratio Test (LRT) method and its extensions, which detect safety signals with reasonable power and sensitivity, and have control of overall type-I error rate and false discovery rate.

The topics covered include the basic LRT method based on Poisson model for safety signal detection in large data without exposure information; Longitudinal LRT methods for active safety surveillance with exposure information; LRT methods for data from multiple studies; LRT method modified for comparing safety issues in treatment vs. control groups using clinical trial data; LRT methods extended for signals in a drug class and a modified LRT method for signals including single drug or drug combinations; ZIP-LRT method for modeling data with extra zero counts; normal-LRT method for continuous outcomes; a spatial-cluster signal detection method using LRT; and the use of LRT in site selection.

We will give demos of the LRT software/tool in OpenFDA for drug and AE signals, and BIMO LRT Inspection Statistical Software (BLISS) for site selection in medical device, both programmed using R and JavaScript, and displayed using Shiny and Shiny dashboard by RStudio (a R package that enables results to be presented in an interactive web application format). The audience will learn the basic concept of LRT methods for safety signal detection in data- mining and its extensions for different applications in drugs and devices, and the use of some R codes on examples for different scenarios.

Session J

Answering Old Questions with New Tools: Application of the ICH E9 Addendum in Oncology

Kaspar Rufibach, Roche and Evgeny Degtyarev, Novartis

Moderator: Kalyan Ghosh

This shortcourse will discuss the application of the ICH E9(R1) estimand addendum to oncology clinical trials. Using examples we will illustrate how the estimand framework supports transparent formulation of clinical trial objective(s) for challenging drug development questions such as

- treatment switching,
- complexity of treatment options and existence of potential curative procedures or treatment sequence across different phases in hematological trials,
- the use of a principal stratum estimand to assess the impact of post-randomization events such as development of antidrug antibodies on efficacy or safety of a new drug.

Often, such type of questions are answered using simplified analyses that are only valid under strong assumptions. To make these assumptions transparent we will discuss estimands, estimation methods, impact on data collection, and experiences with Health Authorities for these scenarios. Finally, we will share our experience in implementing the addendum in large pharmaceutical companies, within biostatistics and for other partner functions.

More on the oncology estimand WG: http://www.oncoestimand.org

Wednesday December 8, 2020 3:30 PM - 6:20 PM

Session K

Statistical Designs and Strategies for Oncology Drug Development

Cong Chen, Merck & Co. Inc

Moderator: Kalyan Ghosh

Following the tremendous success of immune checkpoint inhibitors and other innovative drugs, last few years have witnessed an explosive growth in number of oncology trials. While the expectation is high for the new drugs or vaccines under development, it is unrealistic to expect all of them to have the same success, especially given the improved standard-of-care. It is imperative to apply cost-effective statistical designs and strategies to oncology drug development.

In this short course, I will introduce basket designs for Phase 1B efficacy screening from both statistical and strategic perspectives. I will then talk about how to effectively transition an early oncology program to late-stage development with focus on the 2-in-1 design and its extensions. This will be followed with a discussion of two common issues in design of Phase 3 confirmatory trials :1) how to account for the possible predictive biomarker effect? 2) how to design and monitor trials for combination therapies, leveraging the independent drug action assumption?

Session L

Statistical Methods in the Clinical Development of Novel Cancer Immunotherapies

Bo Huang, Pfizer

Moderator: Naitee Ting

With decades of progress in medical research and advance in understanding the biology of cancer microenvironment, clinical development of novel cancer drugs including immunotherapies and targeted therapies is booming in recent years. In 2018 alone, the FDA approved 19 new cancer drugs and biologics. In 2013, Science names cancer immunotherapy as the scientific breakthrough of the year. Common immunotherapy approaches include cancer vaccine, effector cell therapy and T-cell stimulating antibody. Checkpoint inhibitors such as CTLA-4 and PD-1/PD-L1 antagonists, and CAR-T therapies have shown exciting results in many indications in solid tumors and hematology. However, the mechanisms of action of these novel drugs pose unique statistical challenges in the accurate evaluation of clinical safety and efficacy, such as late-onset toxicity, dose optimization, evaluation of combination agents, biomarkers, non-proportional hazards/delayed efficacy, and estimation of treatment benefit. Traditional statistical methods may not be the most accurate or efficient. It is highly desirable to develop the most suitable methodologies and tools to efficiently develop cancer immunotherapies. In this presentation, I will go over the existing methods, main issues and challenges, and introduce and discuss novel analytical methods to meet the challenges in the clinical development of these drugs.

TWO SHORT COURSES

Registration includes electronic handouts. The book used in the short course is not included in the registration fee. Registrants are responsible to purchase the book themselves. The conference offers a discounted price on book sales. No registrations will be accepted without payment in full. We will refund full tuition if courses are canceled due to insufficient registration.

Daily Schedule: 11:00 AM⇒12:30 PM Lecture/ 12:30 PM ⇒ 1:00 PM *Break*/ 1:00 PM⇒2:30 PM Lecture / 2:30 PM⇒ 2:50 PM *Break* / 2:50 PM⇒4:20 PM Lecture / 4:20 PM⇒4:30 PM *Break* / 4:30 PM ⇒ 6:00 PM Lecture

December 10-11, 2020

Artificial Intelligence for Drug Development, Precision Medicine and Healthcare 🕮

Professor Mark Chang, Boston University
Moderator: Ivan S. F. Chan

Artificial intelligence (AI) or machine learning (ML) has been used in drug discovery in biopharmaceutical companies for nearly 20 years. More recently AI has also been used for the disease diagnosis and prognosis in healthcare. In analysis of clinical trial data, predicted individual patient outcomes for precision medicine, similarity-based machine learning (SBML) has recently been proposed for clinical trials for oncology and rare disease without the requirement of big data.

The course will focus on supervised learning, including similarity-based learning and deep learning neural networks. We will also introduce unsupervised, reinforcement, and evolutionary learning methods. The short course aims at conceptual clarity and mathematical simplicity. Provide *R* code for implementation with examples.

The course materials are based on instructor's book (May, 2020): *Artificial Intelligence in Drug Development, Precision Medicine, and Healthcare*.

Day 1 Course will cover:

(1) A Brief AI History
(2) Classic Statistics versus AI
(3) Artificial General Intelligence Toward Wellbeing
(4) Similarity-Based Machine Learning
(5) Deep Learning: Convolutional Neural Net (CNN)
(6) Deep Learning: Recurrent Neural Net (RNN)
(7) Deep Learning: Deep Belief Net (DBN)
(8) Generative Adversarial Networks & Autoencoders

Day 2 Course will cover:

(1) Kernel Method & Support Vector Machine
(2) Decision Tree Methods
(3) Unsupervised Learning & Applications in Drug Development
(4) Reinforcement Learning & Applications in Clinical Development Program
(5) Collective Intelligence and Applications in Pharmaceutical R &D
(6) Evolutionary Learning & Applications in Drug Discovery
(7) Medical AI: Future Perspectives

Goals: attendees will learn common AI methods in drug development and medicine, be able to use the AI methods with R for clinical trial and other data, and be able to interpret the results.

Dr. Mark Chang is Sr. Vice President, Strategic Statistical Consulting at Veristat. Before joining Veristat, Chang was Vice President of Biometrics at AMAG Pharmaceuticals. Chang is a fellow of the American Statistical Association and an adjunct professor of Biostatistics at Boston University. He is a co-founder of the International Society for Biopharmaceutical Statistics, co-chair of the Biotechnology Industry Organization (BIO) Adaptive

December 14-15, 2020

Working with Generalized Linear and Nonlinear Mixed Models 🕮

Professor Walter Stroup, The University of Nebraska-Lincoln
Moderator: Alfred H. Balch

This course surveys mixed model concepts and methods with a focus on experiments with "mixed model issues" – e.g. various forms of clustering, including repeated measures, split-plot and multi-location studies – in conjunction with "generalized model" issues, i.e. non-Gaussian response variables. Linear and non-linear mixed models are included.

Day One will emphasize essential background ideas and methodology. We start with a survey of the various types of mixed models. We discuss overarching issues that confront analysts who work with correlated, non-normal data, such as overdispersion, marginal and conditional models. We present the various estimation methods for mixed models, and what we have learned to date about their advantages and disadvantages. Examples will be used to illustrate concepts and methods.

Day Two will focus primarily on mixed model applications and on issues associated with these applications. Additional supporting theory will be introduced as needed. We focus both on methods applicable to all mixed models as well as considerations uniquely applicable to specific distribution-model combinations, bearing in mind that different types of data and the different models present particular challenges. Examples will illustrate the difference between pseudo-likelihood and integral approximation estimation algorithms, and when each is preferable. Examples will illustrate the difference between marginal and conditional inference. We will include a "gentle" introduction to Bayesian estimation and inference and discuss differences between Bayesian and frequentist inference. Time permitting, we will discuss additional issues including model selection, model averaging, mixed model-based precision and power analysis, and the use of mixed models for prediction.

Computations will use the mixed model tools in SAS/STAT, primarily the GLIMMIX, NLMIXED and MCMC procedures. No R examples will be presented, but R packages analogous to SAS mixed model procedures will be noted where relevant. The principles in this course should be applicable to any mixed model-capable software. Attendees should have background in statistical design and associated statistical analysis.

Outline

1. **Mixed Model Basics**
   - A. A General Setting for Statistical Modeling
   - B. Types of Mixed Models
     - i. Case 1 – Gaussian (normal) data – linear and nonlinear mixed models (LMM and NLMM)
     - ii. Case 2 – non-Gaussian data – generalized mixed models (GLMM and GNLMM)
   - C. Marginal versus Conditional Models
2. **Modeling Issues**
   - A. Translating Data (design) Structure to Appropriate Model
     - i. Aspect 1 – Model as Characterization of How Data Arise
     - ii. Aspect 2 – Model as Template for Analysis
   - B. Design-Induced Issues
     - i. Overdispersion
     - ii. Within Subject Correlation
   - C. Distributional Issues: Likelihood and Quasi-Likelihood
3. **Estimation and Inference**
   - A. Maximum Likelihood and Residual Maximum Likelihood
   - B. Three Estimation Methods
     - i. Frequentist Method 1: pseudo-likelihood
     - ii. Frequentist Method 2: integral approximation (Laplace and quadrature)
     - iii. Bayesian methods: MCMC, etc.
   - C. Estimable and Predictable Functions
   - D. Inference Approaches
     - i. Frequentist
     - ii. Bayesian
4. **Example Applications 1 – Gaussian (normally distributed) Data**
   - A. Intro example – paired comparison
   - B. Multi-Level Design
   - C. Repeated Measures
   - D. Nonlinear and Smoothing Spline Mixed Models
5. **Example Applications 2 – Count Data**
   - A. Distributions – focus on Poisson and negative binomial
   - B. Intro Example: Blocked Design
   - C. Repeated Measures with Counts

Design Working Group, and a member of the Multiregional Clinical Trial (MRCT) Expert Group. Chang has served associate editor for Journal of Pharmaceutical Statistics. He has been invited to serve as a co-chair on the scientific advisory board and organization committees for several national and international professional/academic conferences on statistics and clinical trial designs. He has given over 50 lectures, short courses, and invited speeches at national and international conferences. Dr. Chang is an expert in adaptive clinical trials and other innovative approach in drug development and has been invited to present adaptive design and biomarker topics at the US Food and Drug Administration. Chang has broad research interests. He has published 10 books, including *Adaptive Design Theory and Implementation Using SAS and R*, *Paradoxes in Scientific Inferences*, *Modern Issues and Methods in Biostatistics*, *Monte Carlo Simulation for the Pharmaceutical Industry*, *Principles of Scientific Methods*, and *Innovative Strategies, Statistical Solutions and Simulations for Modern Clinical Trials*

D. Too many zeroes: Zero-inflated and Hurdle Models
E. Gentle intro to Bayes: Poisson-normal and Poisson-gamma models

6. Example Applications 3 - Proportions

A. Discrete proportions
   i. Binary
   ii. Binomial
   iii. Multinomial
B. Continuous Proportions
C. Beta hurdle models
D. Gentle intro to Bayes continued – Beta-binomial model

7. Additional Issues

A. Model selection and model averaging
B. Using Mixed Models for Planning
   i. Mixed Model Precision and Power Analysis
   ii. Comparing Competing Designs using mixed model tools
C. Inference Issues: Estimation, Hypothesis Testing and Prediction

Walt Stroup is Emeritus Professor of Statistics at the University of Nebraska-Lincoln. He served on the University of Nebraska faculty from 1979 until 2020. His responsibilities included teaching statistical modeling, design of experiments, and research specializing in mixed models and their applications in agriculture, natural resources, medical and pharmaceutical sciences, education, and the behavioral sciences. He is the founding chair of Nebraska's Department of Statistics and served as chair from 2001 until 2010. In 2020, he received the University of Nebraska's Outstanding Teaching and Innovative Curriculum Award, the university's highest teaching honor. He was a member of PQRI's Stability Shelf-Life Working Group from its inception in 2006 until its disbanding in 2019. He received PQRI's *Excellence in Research* award in 2009. He co-authored *SAS for Mixed Models*, *SAS for Linear Models, 4th ed.*, and authored *Generalized Linear Mixed Models: Modern Concepts, Methods and Applications*. He has conducted numerous short courses on mixed and generalized linear models for industry and professional organizations in Africa, Europe, Australia and North America. He is a Fellow of the American Statistical Association.

THREE KEYNOTES

(Monday, Tuesday, and Wednesday Morning, December 7-9, 2020, 11 AM - 12:00 PM)

Keynote 1: Precision Imaging for Precision Medicine- Biomarkers and Beyond

Sue-Jane Wang, FDA

Moderator: Alfred H. Balch

In recent years, the landscape of medical imaging or radiopharmaceuticals is increasingly widening. The large amount of imaging data and the imaging analytical systems allow further quantitative imaging analysis as well as applications of artificial intelligence, machine learning and deep learning. Precision imaging is receiving broad attention. Many imaging measures have been proposed as biomarker tools for therapeutic drug developments. There is also a growing interest in integrating imaging and therapeutic drug developments. We are witnessing the growing clinical utilities of medical imaging and imaging radiopharmaceuticals. In this presentation, the advances in these areas from scientific underpinning and regulatory consideration on tangible benefits with newer developments and design considerations will be highlighted.

*The views expressed are those of the author and should not be construed to represent the views or policies of the U.S. Food and Drug Administration.

Keynote 2: Harnessing the Power of Statistics: Big Challenges, Big Opportunities

Dione Price, FDA

Moderator: Naitee Ting

Ebola, antibiotic drug resistance, rare diseases, and COVID-19 are only a few of the many areas that have demanded global attention in recent years. While these areas have created immense challenges, they have also resulted in vast opportunities. From a global pandemic to ongoing oncology demands, the need to harness the power of statistics has become ever more apparent. Statisticians are taking the lead in designing and analyzing clinical trials for potential therapeutic agents that will further advance our public health. Statisticians are employing innovative approaches that will allow clinical trials to efficiently and reliably answer questions of interest.

The Food and Drug Administration (FDA) has been at the forefront of meeting the challenges arising from the evolving needs of patients. FDA statisticians play a vital role in diverse topics such as real-world evidence, patient-focused drug development, model informed drug development, and complex innovative trial designs. This talk will provide an overview of how the power of statistics is being harnessed at the FDA and beyond, with a specific focus on complex innovative trial designs.

Keynote3: New Statistical Initiatives in the FDA CDRH

Ram Tiwari, CDRH, FDA

Moderator: Bill Wang

In this keynote, I will present some innovative Frequentist/Bayesian statistical methods that supports the CDRH mission for development of first of its kind in the world, safe, and effective medical devices. These methods include: i) leveraging information from a real-world data (RWD) source to construct or augment the control arm or a single-arm in an investigational clinical study, ii) benefit-risk assessment for a therapeutic or a diagnostics device, iii) likelihood-ratio-test (LRT) based signal detection methods for large safety databases, and iv) a site-selection tool for inspection.

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Three Day Conference (December 7-10)	$250 ❑	$375 ❑	
Student (Full time status proof needed) or Retiree	$125 ❑	$275 ❑	
Two Day Short Course (December 11-12) ❑ Working with Generalized Linear and Nonlinear Mixed Models ❑ Artificial Intelligence for Drug Development, Precision Medicine and Healthcare	 $375 ❑ $375 ❑	 $425 ❑ $425 ❑	

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*SAS for Mixed Models: Introduction and Basic Applications, by Walter W. Stroup, George A. Milliken, and Elizabeth A. Claassen	608	2018	978-1642951837	125.05	35%

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