ICSA 2017 Applied Statistics Symposium Short Courses

SC01 Multi-Regional Clinical Trials for Simultaneous Global New Drug Development
Instructors: Joshua Chen (Sanofi Pasteur), Hui Quan (Sanofi)
Course Length: half-day

Outline/Description:

Global clinical development strategy utilizing multi-regional clinical trials (MRCTs) plays a crucial role in developing innovative medicines. It is readily accepted that studying patients from many different regions within a single trial under a single protocol is an efficient method of trial design. The prevalence of these trials has been growing over the last few decades. MRCTs are most often conducted as a single trial focusing on the overall results, but when such trials are submitted to health authorities, the scope and concern often broaden to include the "local" results. Therefore, together with great opportunities, there are also tremendous challenges in the design, conduct and interpretation of MRCTs.

This short course is intended to provide a comprehensive view of the current status of conducting MRCTs in clinical development. We will start with the motivation, opportunities and challenges in simultaneous global clinical development using MRCTs. We then will focus on the design, monitoring and analysis/interpretation of MRCTs. These include the discussion of region definitions, the scenarios where different regions have differing requirements for a MRCT, the comparisons of models for MRCT, the quantifications of regional treatment effects, and methods for the assessment of consistency of regional treatment effects. Simulations and trial examples will be used to illustrate the ideas, methods and thinking.

The registration fee for this short course includes a copy of the following book at a discounted rate.

Reference:

[1] Josh Chen, Hui Quan (2016). Multiregional Clinical Trials for Simultaneous Global New Drug Development. April 2016. Chapman and Hall/CRC.

About the Instructors:

Dr. Yonghua (Joshua) Chen received his PhD in Statistics from the University of Wisconsin-Madison. He is currently the Global Head of Biostatistics and Programming at Sanofi Pasteur. Before joining Pasteur, Josh worked on clinical development of small molecules, biologics and vaccines at Merck Research Laboratory Labs. His experience spans many therapeutic areas with major focus on human vaccines and antiviral drugs. He has extensive experience in study design, conduct and reporting of international clinical trials from proof-of-concept through regulatory approvals and life cycle management. His primary research interest is clinical trial designs, including group sequential methods, adaptive designs and multiregional clinical trials

(MRCTs). He was a co-lead of the across-industry MRCT Consistency Working Group under PhRMA (2008-2011) and Society for Clinical Trials (2012-2014). He is a fellow of the American Statistical Association.

Dr. Hui Quan received his PhD degree in statistics from Columbia University in 1990. He is currently an associate VP and Global Head of the methodology group at the Biostatistics and Programming Department of Sanofi. He has 26 years of pharmaceutical industry experience in many therapeutic areas ranging from early phase to Phase IV studies. He has published 89 papers including 66 statistical papers. His research interests include multivariate analysis, safety analysis, multiplicity adjustment, missing handling, adaptive design, integrated data analysis, modeling and simulation, benefit/risk assessment and multi-regional clinical trials (MRCT). He served as a co-leader of the MRCT consistency assessment working group under PhRMA (2008-2011) and Society for Clinical Trials (2012-2014). He was elected as a fellow of the American Statistical Association in 2008.

SC02 Methods of biomarker and subgroup identification for personalized medicine
Instructor: Ilya Lipkovich (Advisory Services, QuintilesIMS)
Course Length: half-day

Outline/Description:

This short course will provide a description of a broad class of statistical methods dealing with exploratory subgroup analysis, i.e., subgroup search/biomarker discovery methods that can be applied both in early and late-phase clinical trials. We will also talk briefly about applying these methods in the context of non-randomized (observational studies). Discussion of exploratory subgroup analysis methods begins with a broad review of existing approaches to subgroup/biomarker identification in the context of personalized medicine and then focuses on the SIDES method (Lipkovich *et al*., 2011) and its extensions SIDEScreen and Stochastic SIDEScreen (Lipkovich and Dmitrienko, 2014, Lipkovich *et al*, 2017). SIDES is based on recursive partitioning and can be used in prospective and retrospective subgroup analysis of clinical trials. Key elements of SIDES and SIDEScreen will be discussed, including (1) generation of multiple promising subgroups based on different splitting criteria, (2) evaluation of variable importance (VI) and implementing VI-based biomarker screening, and (3) addressing Type I error rate inflation using a resampling-based method.

Case studies from both early and late clinical development programs will be used to illustrate the principles and statistical methods introduced in this course. A software tool for exploratory subgroup analysis will be presented (RSIDES package developed by the authors).

References:

[1] Lipkovich, I., Dmitrienko, A., Denne, J., Enas, G. (2011). Subgroup Identification based on Differential Effect Search (SIDES): A recursive partitioning method for

establishing response to treatment in patient subpopulations. Statistics in Medicine. 30, 2601-2621.

[2] Ilya Lipkovich and Alex Dmitrienko (2014). Strategies for Identifying Predictive Biomarkers and Subgroups with Enhanced Treatment Effect in Clinical Trials Using SIDES. Journal Of Biopharmaceutical Statistics Vol. 24 , Iss. 1,2014

About the Instructor:

Ilya Lipkovich, Ph.D., is Principal Scientific Advisor, Advisory Services at QuintilesIMS. He received his Ph.D. in Applied Statistics from Virginia Polytechnic Institute and State University in 2002. He has more than 15 years of statistical consulting experience working in areas including econometrics, manufacturing and quality control, and pharmaceutical industry. He joined Quantiles in 2012. His research interests include clustering, predictive modeling and subgroup identification in clinical data, analysis with missing data, and causal inference from observational data. Ilya is a co-developer of novel subgroup identification methods (SIDES and SIDEScreen) and chairs the QSPI Subgroup Analysis Working Group sponsored by the Society of Clinical Trials.

SC03 Bayesian Adaptive Clinical Trials in the 21st Century

Instructor: Ben Saville (Berry Consultants and Vanderbilt University Dept. of Biostatistics)
Course Length: half-day

Outline/Description:

As medical research continues to push into new frontiers of discovery and personalized patient care, it is imperative that clinical trial designs and statistical methodologies evolve to address the forthcoming challenges. In this course we discuss why Bayesian adaptive clinical trial designs are ideally suited to provide such innovation, with particular emphasis in phase II and III medical drug/device trials. Innovations include historical borrowing, hierarchical models, adaptive sample size with interim monitoring, Bayesian predictive probabilities, seamless transitions to subsequent phases, and multi-arm platform trials with a master protocol. I illustrate these methods using real clinical trial examples, and show the importance of simulations in navigating the regulatory environment. Hands-on small group activities are used to encourage discussion and learning.

About the Instructor:

Ben Saville is a Statistical Scientist for Berry Consultants, where he specializes in the design of innovative Bayesian adaptive clinical trials. He works primarily with medical device companies, pharmaceutical companies, and academic investigators to solve challenging problems via Bayesian designs, many of which are reviewed by the U.S. Food and Drug Administration (FDA). He is a frequent invited speaker at various statistical conferences, academic seminars, and lecture series, including short courses on adaptive clinical trial design. Dr. Saville earned his Ph.D. in Biostatistics from the University of North Carolina at Chapel Hill in 2008. Prior to

joining Berry Consultants in 2014, he was an Assistant Professor of Biostatistics at Vanderbilt University School of Medicine where his methodological research focused on Bayesian hierarchical models, Bayesian adaptive clinical trials, and nonparametric methods for randomized clinical trials. At Vanderbilt, he collaborated extensively with medical researchers in the Department of Pediatrics and the Vanderbilt-Ingram Cancer Center, and was co-leader of an adaptive trials design workforce to promote innovative Bayesian methodology in clinical trials. In addition, he taught undergraduate and graduate courses in the Department of Biostatistics and Department of Biomedical Engineering. Dr. Saville has authored over 50 peer-reviewed publications in the statistical and medical literature.

SC04 Statistical methods and software for multivariate meta-analysis
Instructors: Haitao Chu (Univ of Minnesota), Yong Chen (Upenn)
Course Length: half-day

Outline/Description:

This short course will provide an overview and tutorial of the cutting edge statistical methods and software for meta-analysis of diagnostic tests and multiple treatments comparisons. In particular, statistical models and methods will be presented in nontechnical format so that the course materials will be understood by applied statisticians. The short course will be presented with many case studies with detailed study background, well-formatted data sets, and relevant SAS and WinBUGS/R codes. Those details will enable audiences to understand the benefits of applying those innovative statistical methods developed recently, and to be able to apply those models in practice. Emphasis is given on the intuition behind those models and how to communicate the significance of applying those models with clients and customers. In return, those innovative methods and case studies will allow the audiences to achieve better estimation in meta-analysis of the accuracy of diagnostic tests and network clinical trials with multiple treatments.

About the Instructors:

Dr. Haitao Chu, Associate Professor of Biostatistics at the University of Minnesota. His methodology research focuses on comparative effectiveness research, meta-analysis and diagnostic test accuracy studies, and he has been working on meta-analysis for more than ten years. He has published over 140 peer-reviewed manuscripts, including over 30 on systematic reviews and meta-analysis in top ranked statistical and medical journals such as *JASA*, *Biometrics*, *SIM*, *SMMR*, *Clinical Trials*, *JNCI*, *AIDS* and *AJE*, and coauthored four R packages *pcnetmeta, altmeta, xmeta* and *mmeta*. Dr. Chu's research on meta-analysis has been supported by FDA, AHRQ, NIAID, NIDCR and NLM. Dr. Chu is an ASA Fellow and elected member of the Society for Research Synthesis Methodology.

Dr. Yong Chen, Assistant Professor of Biostatistics at the University of Pennsylvania, has been working on the field of meta-analysis since 2008. He has published over 50 peer-reviewed

manuscripts, including 15 on statistical methods for meta-analysis in top statistical journals such as *Biometrics*, *JRSS-C, SIM* and *SMMR*. He is also one of the main contributors of the R package for multivariate meta-analysis of binary data *mmeta* and package for multivariate meta-analysis that accounts for publication bias for continuous and binary data *xmeta*. His research has been supported by both AHRQ and NIH.

SC05 Clinical Trials for Time-to-Event Outcomes: Current Practice and New Developments
Instructor: Song Yang (NIH)
Course Length: half-day

Outline/Description:

Clinical trials assess the safety and effectiveness of new diagnosis, treatment, or prevention strategies. Very often the relevant outcome is a time-to-event outcome. While many time-honored statistical tools, such as the log-rank test and Cox model inference, have been the cornerstones for time-to-event data analysis, many new methods have been developed in recent years. However, the systematic introduction of these new methods and their incorporation into clinical research practice has been rare. Adding to the complication and confusion is the fact that some approaches are more appropriate for exploratory studies while others are more appropriate for confirmative clinical research. The first part of the proposed short course would cover essential tools for clinical trials with time-to-event outcomes, such as sample size and power calculation, the log-rank test and its variations, interim analysis, and hazard ratio estimation. In the second part, we would go beyond the usual toolbox of the log-rank test and Cox model inference and look at cutting-edge developments that improve and expand the current practice, working with alternative models and measures for the outcomes to increase the flexibility, efficiency, applicability, and generalizability of clinical trial research. Depending on the audience, specific topics of this short course would include (i) clinical trial design, sample size and power calculation, (ii) the log-rank test and its variations, (iii) interim analysis, (iv) hazard ratio estimation, (v) time-dependent treatment effect, (vi) average hazard ratio and superiority probability, (vii) absolute risk reduction and restricted mean survival, (viii) covariate-adjusted analysis, and (ix) other measures and models. Applications to clinical trials, including some of the well-known large trials, will be illustrated using R so that the attendees will be able to understand the implementation procedures and analyze their own research data.

References:

[1] Kalbfleisch, J. D. and Prentice, R. L. (2011). *The Statistical Analysis of Failure Time Data*, Second Edition, Wiley.

[2] Yang, S. and Prentice, R. L. (2010). Improved logrank-type tests for survival data using adaptive weights. *Biometrics*, 66: 33-38.

[3] Yang, S. and Prentice, R. L. (2015). Assessing potentially time-dependent treatment effect from clinical trials and observational studies for survival data, with

applications to the Women's Health Initiative combined hormone therapy trial. *Stat, in Med.* 34(11):1801-1817.

About the Instructor:

Song Yang (Ph.D., Michigan State University, 1987) is a senior mathematical statistician and program officer at the Office of Biostatistics Research, National Heart, Lung, and Blood Institute, NIH. Before joining NIH, Dr. Yang was a full professor and the Statistics Coordinator at Texas Tech University. His major research interests are survival analysis and clinical trials. In the last 30 years, Dr. Yang has published numerous articles in methodology research and applied research in journals such as *Ann. Statist., Biometrics, Biometrika, JASA, Stat. in Med.,* and *NEJM.* He is also a frequent reviewer for these journals and for National Science Foundation proposals, and has co-authored the R package YPmodel. Dr. Yang has given numerous invited presentations at major conferences and university seminars. He is an associate editor for *Lifetime Data Analysis* and *Stat. & Prob. Lett.,* a guest lecturer of the Foundation for Advanced Education in the Sciences at NIH, and a past guest co-editor for *Stat. in Med.* Since joining NIH, Dr. Yang has served as the project office statistician of a dozen large-scale clinical trials and studies and has received the NIH Director's Award and many other NIH awards for his service.

SC09 Integrative Multivariate Statistical Learning in Healthcare Research with Real-World Data

Instructor: Kun Chen (Univ of Connecticut), Dingfeng Jiang (AbbVie)
Course Length: half-day

Outline/Description:

This short course starts with an overview of recent problems arising from healthcare studies with large-scale heterogeneous data; examples include pragmatic trial, drug development, outcome research, suicide prevention, and opioid abuse. In these problems, a common scheme is that measurements of several distinct yet interrelated characteristics pertaining to a single set of subjects are collected from an array of disparate sources. For example, individual health data may come from insurance claims, pharmacy visits, clinical records, patient surveys, and government statistics. The availability of such complex data makes tackling many scientific and practical problems possible through "integrative statistical learning", which is undergone exciting development and is pushing for a refinement of the conventional multivariate learning toolkit. In this short course, several classes of multivariate learning techniques for simultaneous dimension reduction, feature selection and model estimation will be introduced, together with discussions of several practical case studies in healthcare. The course consists of 4 modules: 1) overview of problems and statistical challenges in healthcare studies with big data; 2) integrative multivariate data reduction techniques with case studies; 3) integrative predictive modeling techniques with case studies; 4) recent developments on multi-view data fusion. The participants will have the opportunity to go through examples using newly developed R packages.

About the Instructors:

Dr. Kun Chen is an Assistant Professor in the Department of Statistics, University of Connecticut (UConn), and a Research Fellow at the Center for Public Health and Health Policy, UConn Health Center. Chen's research interests include multivariate statistical learning, high-dimensional statistics, and health informatics with large-scale heterogeneous data. He has extensive interdisciplinary research experience in a variety of fields including insurance, ecology, biology, agriculture, medical imaging, and public health. Chen's research projects have received funding from the National Institutes of Health, the Simons Foundation, the National Science Foundation, etc. Currently he is involved in a data-driven suicide prevention study through integrating big data from disparate sources. Chen was a Co-Editor of the 2015 ICSA Symposium Proceeding Book, and serves as an Associate Editor of *Sankhya: The Indian Journal of Statistics* since 2016. He was recognized for Teaching Excellence at UConn for multiple times.

Dr. Dingfeng Jiang is a statistical manager at AbbVie Inc. Jiang's research interest include high-dimensional statistics, variable selection, and causal inference in observational studies. He has extensive research experience in designing observational outcome research using big healthcare data, with application in diabetes, oncology and immunology therapy areas. He has served as reviewers for multiple statistical journals. He is an editorial board member for *Heliyon,* an open access journal published by Elsevier.

SC10 Phase II Clinical Development
Instructors: Naitee Ting (Boehringer Ingelheim), Shuyen Ho (Parexel)
Course Length: half-day

Outline/Description:

Clinical development of new drugs or new biologics can be broadly divided into four phases - Phases I, II, III, and IV. Phase I is primarily to study the pharmacokinetics (PK) properties and to estimate maximally tolerable dose (MTD) and Phase II is for proof of concept (PoC) and dose ranging. Phase III is designed and executed for registration and Phase IV is for post marketing purposes. Because product efficacy is not the focus of Phase I, Phase II is typically the first time drug efficacy is tested in patients with the targeted disease. After Phase II, a major decision will be made for the progressing of test product into Phase III or not. Therefore Phase II can be considered as the most critical phase in clinical development. This course emphasizes the importance and challenges of Phase II development, examples and case studies are illustrated to provide guidance on Phase II study designs and analysis methods.

About the Instructors:

Naitee Ting is a Fellow of ASA. He is currently a Director in the Department of Biostatistics and Data Sciences at Boehringer-Ingelheim Pharmaceuticals Inc. (BI). He joined BI in September of 2009, and before joining BI, he was at Pfizer Inc. for 22 years (1987-2009). Naitee received his

Ph.D. in 1987 from Colorado State University (major in Statistics). He has an M.S. degree from Mississippi State University (1979, Statistics) and a B.S. degree from College of Chinese Culture (1976, Forestry) at Taipei, Taiwan. Naitee published articles in Technometrics, Statistics in Medicine, Drug Information Journal, Journal of Statistical Planning and Inference, Journal of Biopharmaceutical Statistics, Biometrical Journal, Statistics and Probability Letters, and Journal of Statistical Computation and Simulation. His book "Dose Finding in Drug Development" was published in 2006 by Springer, and is considered as the leading reference in the field of dose response clinical trials. The book "Fundamental Concepts for New Clinical Trialists", co-authored with Scott Evans, was published by CRC in 2015. Naitee is an adjunct professor of Columbia University, University of Connecticut and University of Rhode Island. Naitee has been an active member of both the American Statistical Association (ASA) and the International Chinese Statistical Association (ICSA).

Shuyen Ho is a Biostatistics Director at PAREXEL International in Durham, North Carolina. Shuyen has worked in the pharmaceutical industry for 27 years. Prior to PAREXEL, he was a Clinical Statistics Director at GlaxoSmithKline (GSK) and Group Leader at Merck. He specializes in Phase II & III clinical development and has helped developed widely used respiratory medicines such as Claritin, Advair and Veramyst. Shuyen received his PhD in Statistics from University of Wisconsin – Madison, and his Bachelor in Applied Mathematics from Taiwan.

SC11 Principles of Multiple Comparisons, with Applications
Instructors: Jason C. Hsu (OSU), Frank Bretz (Novartis), Yi Liu (Tekeda), Dong Xi (Novartis)
Course Length: half-day

Outline/Description:

Two main principles provide the foundation of multiple testing: Closed testing and partitioning. Most multiple comparison methods can be derived and their validity can be proven using these two principles. In this course we show how they are connected using several examples.

Starting with realistic numerical examples, the first and conceptual part of this short course will show that the traditional methods of Holm, Hochberg, and Hommel are special cases of closed testing and partitioning. To give insight into how the partitioning principle simplifies challenging problems, we show how Hsu and Berger (1999) formulated the problem of testing multiple doses in a pre-determined step-wise fashion to guarantee decision-making following a pre-specified path. We then show how Liu and Hsu (2009) applied the same path partitioning principle to simplify testing with multiple paths, such as testing for efficacy in multiple doses in combination with multiple endpoints. To conclude the first part of the course, we show how the gatekeeping method of Xu et al (2009), the graphical approach of Bretz et al (2011), and the partition testing principle of Liu and Hsu (2009) coincide and rely on the same testing principles.

The second part of this short course will be on the graphical approach's flexible and transparent implementation of multiple testing. Using graphical approaches (Bretz et al, 2009), one can

easily construct and explore different test strategies and thus tailor the test procedure to the given study objectives. The resulting multiple test procedures are represented by directed, weighted graphs, where each node corresponds to an elementary hypothesis, together with a simple algorithm to generate such graphs while sequentially testing the individual hypotheses. We also present one case study to illustrate how the approach can be used in clinical practice. The presented methods will be illustrated using the graphical user interface from the gMCP package in R, which is freely available on CRAN.

References:

[1] Hsu, Jason C. and Berger, Roger L. (1999). Stepwise Confidence Intervals without Multiplicity Adjustment for Dose-Response and Toxicity Studies. *Journal of the American Statistical Association*, 94: 468-482.

[2] Liu, Yi and Hsu, Jason C. (2009). Testing for efficacy in primary and secondary endpoints by partitioning decision paths. *Journal of the American Statistical Association*, 104: 1661-1670.

[3] Xu, Haiyan and Nuamah, Isaac and Liu, Jingyi and Lim, Pilar and Sampson, Allan. (2009). A Dunnett-Bonferroni-based parallel gatekeeping procedure for dose-response clinical trials with multiple endpoints. *Pharmaceutical statistics*, 8: 301-316.

[4] Bretz, Frank and Posch, Martin and Glimm, Ekkehard and Klinglmueller, Florian and Maurer, Willi and Rohmeyer, Kornelius. (2011). Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biometrical Journal*, 53: 894-913.

[5] Bretz, Frank and Maurer, Willi and Brannath, Werner and Posch, Martin. (2009). A graphical approach to sequentially rejective multiple test procedures. *Statistics in medicine*, 28: 586-604.

About the Instructors:

Jason Hsu is an emeritus professor in the Department of Statistics of the Ohio State University. His recent research on multiple comparisons focuses on efficacy inference in subgroups and their mixtures, both in discovery studies and in confirmatory studies.

Frank Bretz joined Novartis in 2004, where he is currently Global Head of the Statistical Methodology and Consulting group. He has supported the methodological development in various areas of drug development, including dose-finding, multiple comparisons, and adaptive designs.

Yi Liu earned her PhD from department of statistics at the Ohio State University in 2009. She currently works as a senior manager in the department of global statistics and programming at Takeda Pharmaceuticals Inc. Her research interests include adaptive designs and multiple comparisons.

Dong Xi joined Novartis in 2013, where he is an Expert Statistical Methodologist in the Statistical Methodology and Consulting group. His research interests include multiple

comparisons and dose-finding. Prior to his current role, he got his PhD in statistics from Northwestern University.

SC12 Bayesian Adaptive Phase I Oncology Trials: Methodology and Implementation methodology

Instructors: Satrajit Roychoudhury (Novartis), Beat Neuenschwander (Novertis)
Course Length: half-day

Outline/Description:

Phase I trials in Oncology are usually small adaptive dose-escalation trials. The aim is to approximately understand the dose-toxicity profile of a drug, and, eventually, to find a reasonably safe dose for future testing. A lot of statistical research for Phase I trials has accumulated over the past 25 years, with modest impact on statistical practice. The vast majority of trials still follow the 3+3 design, despite the fact that it often misses the targeted dose (poor operating characteristics) and fails to provide a real understanding about true toxicity rates (no statistical inference).

In this course we present a comprehensive and principled statistical approach. The implementation is Bayesian, with the following main parts: a parsimonious model for the dose-toxicity relationship; the possibility to incorporate contextual information ("historical data") via priors; and, safety-centric metrics (overdose probabilities) which inform dose adaptations under appropriate overdose control.

After some basic clinical and statistical considerations, we introduce the statistical methodology for the single-agent setting, and then extend it to dual- and triple-combinations. Applications and a discussion about implementation (such as basic WinBUGS code) issues complement this training and provide practical insights into Phase I trials.

References:

[1] Rogatko, Schoeneck, Jonas et al. Translation of innovative designs into phase I trials. JCO 2007.

[2] Neuenschwander, Matano, Tang, Wandel, Roychoudhury and Bailey. A Bayesian Industry Approach to Phase I Combination Trials in Oncology. *Statistical Methods in Drug Combination Studies*, Boca Raton, FL: Chapman & Hall/CRC Press 2015.

[3] Neuenschwander, Branson, Gsponer. Critical aspects of the Bayesian approach to phase I cancer trials. StatMed 2008.

[4] Neuenschwander, Capkun-Niggli, Branson, Spiegelhalter. Summarizing historical information on controls in clinical trials. Clinical Trials 2010.

[5] Schmidli, Gsteiger, Roychoudhury, O'Hagan, Spiegelhalter, Neuenschwander. Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics 2015 (accepted).

About the Instructors:

Dr. Satrajit Roychoudhury is Director and member of Statistical Methodology and Consulting at Novartis Pharmaceuticals, USA. Before joining Novartis in 2009, he was at Schering Plough Research Institute. He has a strong expertise in interacting with statisticians, clinicians and scientists regarding implementation of innovative statistical methodology in clinical trial. He has extensive experience of development and implementation of model based approaches in Phase I Oncology trials. He co-authored several publications/book chapters in this area. He also provided half-day training on similar topic at Joint Statistical Meeting, Seattle and ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop, Washington D.C. in 2015. In addition he has 5 years of extensive experience in working with different phase clinical trials. His area of research includes the use of Bayesian methods in clinical trials, especially evidence synthesis. He authored several publications in peer reviewed journals and served as a referee for many journals. He is currently working on and is currently working on the book "Statistical Challenges in Oncology Drug Development" (CRC Press).

Dr. Beat Neuenschwander received his Ph.D. in 1991 from the University of Bern, Switzerland. From 1992 to 2000, he had a joint appointment as a consultant and statistical analyst at the Department of Social and Preventive Medicine, University of Berne, and the Department of Epidemiology, Swiss Federal Office of Public Health. He joined Novartis Pharmaceuticals in 2001, where he worked as a trial statistician, statistical modeler, and methodologist. He joined the Novartis Oncology Business Unit as a Biometrical Fellow in 2010. Beat Neuenschwander has contributed significantly to the methodological development in various areas of drug development, including the design of Bayesian phase I cancer trials, and the use of historical data in Phase I and II clinical trials. During the past 20 years in academia and industry, he has given various Bayesian trainings. He served as an associated editor for Biometrical Journal. He has authored or co-authored 30 articles in peer-reviewed journals, and is currently working on the book "Bayesian Reasoning in Drug Development" (Springer) with his colleague Heinz Schmidli (Novartis Pharma).

SC13 Design and Analysis of Real-world Clinical Studies Using SAS and R
Instructor: Macaulay Okwuokenye (Biogen)
Course Length: half-day

Outline/Description:

Although randomized, controlled, double blind experiments (RCDBE) are considered the gold standard for evidentiary inference, many instances exist where a RCDBE may be unethical or impractical. Moreover, a RCDBE may not be reflective of real-world settings. Such instances may warrant reliance on data from studies from more practical designs to support decision and policy making—e.g., strengthening comparative effectiveness profile of a therapeutic product or medical device using data from routine clinical practice or disease registries. The design, conduct, and statistical analyses of departures from the RCDBE can and should mirror randomized counterpart. Departures could include non-randomized, non-controlled, non-double blinded, or any combination of these. Participants will learn methods for designing credible real-world clinical studies that mimic traditional randomized trials, and statistical

analysis of data therefrom. These methods derive from causal inference framework, including propensity score (matching, inverse probability of treatment weight, stratification by propensity score), genetic matching, etc. Best methodological practices for improving credibility of findings will be discussed. Software implementation of these methods using SAS and R will be demonstrated.

About the Instructor:

Macaulay Okwuokenye is a Principal biostatistician at Biogen Inc., MA and an adjunct faculty of biostatistics at Jiann-Ping Hsu College of Public Health (JPHCOPH), Georgia Southern University, GA. At Biogen, he supports design, conduct, and analyses of clinical trials and real-world clinical studies and exploratory data analysis. He has years of academic research and several years of clinical research, statistical consultation, and pharmaceutical and biotechnology industry experience spanning phase II, IV, registries, real-world, and bioequivalence studies. Macaulay is adept in evidentiary inference for real-world data and comparative effectiveness of therapeutic products. He received the masters and doctoral degree in biostatistics from the JPHCOPH, Georgia Southern University. He has published in methodological and applied international journals and is a reviewer for international statistical journals. He is a speaker at international conferences, statistical workshop, and academic seminars.

SC14 Experiences and Case Studies in Adaptive Clinical Trial Design
Instructors: Shiowjen Lee (FDA), Min (Annie) Lin (FDA)
Course Length: Half-day

Outline/Description:

For the past decades, there has been considerable interest among pharmaceutical and other medical product developers in adaptive design clinical trials, in which knowledge learned from data of an ongoing trial affects design features or analysis of the study. Following the release of the FDA draft Guidance document on adaptive design clinical trials in early 2010, there have been high expectations of an increase in regulatory submissions involving adaptive design features, particularly for confirmatory trials. Additionally, the recently passed 21st Century Cures Act encourages a broader use of adaptive design in clinical studies. Despite all this, there remain some concerns and questions regarding statistical analyses and operational challenges in conducting adaptive design clinical trials. We will share our experiences in the review of adaptive design proposals, including surveys performed regarding regulatory submissions of adaptive design proposals as well as case studies which have been reviewed. We will also provide general recommendations for developing proposals for such trials. Our motivation in instructing this short course is to encourage the best study design proposals to be submitted to FDA. Sometimes these designs can be adaptive and sometimes a simpler design is most efficient.

About the Instructors:

Shiowjen Lee, Ph.D. is currently Team Leader in Center for Biologics Evaluation and Research (CBER), US FDA. In her current role, Dr. Lee oversees regulatory submissions supporting the biologic products of tissue, cellular and gene therapies regulated by Office of Tissue and Advanced Therapies (OTAT). Prior to the current role, she has worked at Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH) as a Mathematical Statistician in reviews of regulatory submissions. In her work, she has been reviewing a wide range of regulatory applications including cancer vaccines, anti-inflammatory products, products (including biologic and devices) to treat cardiovascular disease, rare disease and many others. She has expertise in both statistics and clinical trial design and has broad experiences in products regulated at different Centers in FDA. Dr. Lee's work in FDA has also included developing regulatory guidance and policies regarding specific indications, and statistical issues. She has a great ability collaborating and communicating statistics to review teams and non-statisticians. Dr. Lee has been a recipient for numerous awards at Center and FDA levels in FDA including Outstanding Service award, Team Excellence award, Center Director's Award for Improving Communication, Managerial Excellence award, and many others. She was a Co-Chair of 2014 FDA/Industry Statistics Workshop that was held at Washington DC.

Min (Annie) Lin, Ph.D. joined the Division of Biostatistics at Center for Biologics Evaluation and Research (CBER), US FDA in 2011 as a Mathematical Statistician with special focus on Adaptive Designs. In her current role, Dr. Lin performs critical statistical reviews of regulatory pre-marketing submissions to the Office of Tissues and Advanced Therapies (OTAT) and participates in regulatory guidance development. She supervises the FDA interns in conducting biostatistical methodology researches in the area of adaptive designs that are related to CBER regulated biologics products and medical devices. Prior to joining the FDA, Dr. Lin was an Assistant Professor in the Department of Biostatistics and Bioinformatics at Duke University School of Medicine. She served as statistical investigator/co-investigator in various pharmaceutical-funded and government-funded studies for a wide range of therapeutic areas.

SC15 Quantitative Sciences for Safety Monitoring during Clinical Development
Instructors: Susan Duke, Krishan (KP) Singh, Wenquan Wang, Ed Whalen, On Behalf of the ASA Safety Monitoring Working Group
Course Length: Full-day

Outline/Description:

In an effort to better promote public health and protect patient safety, there is growing interest in developing a systematic approach for safety evaluation of pharmaceutical products, not only for post-marketing safety surveillance, but also for pre-marketing safety monitoring. Recent regulatory guidance, such as CIOMS VI, ICH E2C and FDA IND safety reporting guidance (2012, 2015), have highlighted the importance and given recommendations on aggregate safety monitoring. Biostatisticians and other quantitative scientists can closely engage with clinical and regulatory scientists and play a vital role in these efforts. In 2015, to better enable this, the ASA Biopharmaceutical Section established a working group on clinical safety monitoring.

This tutorial session will present the work that has been done by this ASA safety monitoring working group, in two parts: 1. Summary of relevant regulatory guidance and results of an industry-wide survey on current process and technology enablement. 2. Discussion of various statistical methods for safety monitoring , these include blinded vs unblinded analyses, Frequentist vs Bayesian approaches, premarketing vs post marketing strategies, static vs dynamic assessments, trial-level vs program-level data aggregations, as well as visual analytical methods for safety data monitoring.

A continual theme throughout the day will be the opportunity for quantitative scientists to engage in understanding the safety challenges and help provide solutions for colleagues in the broader safety surveillance fields. Audience participation will be highly encouraged.

About the Instructors:

Susan Duke joined AbbVie in early 2016 as director and head, Safety Statistics in Data Science and Statistics. Beginning at Genentech in 1986, she held positions at small biotech/device companies, followed by 18 years at GlaxoSmithKline, completing her tenure there in Benefit-Risk Evaluation in the Drug Safety department. In her 30th year in industry, her most notable achievements have been in safety graphics, quantification of benefit-risk processes and deliverables, and a track record for successfully implementing new ways of working across multiple disciplines.

Krishan Singh has been working in the pharmaceutical industry for 29 years, starting at Smith Kline & French which subsequently became GlaxoSmithKline following M&A. In his 29 years in the industry as a statistician, he has supported clinical development of drugs across a number of therapy areas leading to regulatory submissions and market authorization of six new drugs in cardiovascular, inflammation and tissue repair, anti-infectives, respiratory and rare diseases. Krishan brings extensive experience in the application of statistical methodologies for the evaluation of safety and efficacy of investigational drugs.

Wenquan Wang has been working in the clinical development for 13 years, mainly in oncology. He has worked for GlaxoSmithKline, Eisai, and currently Morphotek. He has worked on chemotherapeutic agents, cancer supportive care, and monoclonal antibodies as add-on to chemo-backbone or maintenance therapy, in which benefit risk balance is always a critical point in evaluating these drugs. Wenquan has particular interest in evaluating anti-drug-antibodies when patients are treated with monoclonal antibodies.

Ed Whalen has worked in the biopharma industry for 25 years, six at Bayer Inc and 19 at Pfizer Inc. He has worked in anti-infectives, oncology, cardiovascular, neuroscience, and pain. For the last 15 years his work has focused on neuroscience and pain. Because of the variability in patient efficacy response, Ed has ventured into safety statistics to better understand the benefit risk balance for these drugs and in general.