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

Sponsored by
AMERICAN SOCIETY FOR QUALITY
NY/NJ Metropolitan Section ~ Statistics Division
ASA: Biopharmaceutical Section
December 5 – December 7, 2016: Three-Day Conference
Tropicana Casino and Resort, Havana Tower, Atlantic City, NJ

Short Courses: – December 8-9, 2016

1. Adaptive Designs and Multiple Testing (**Martin Posch** & **Franz Koenig**, Medical University of Vienna; **Frank Bretz**, Novartis
2. Bioequivalence, Biosimilars and Statistics in Clinical Pharmacology (**Scott Patterson**, Pfizer, **Byron Jones** & **Johanna Mielke**, Novartis)

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

ONSITE REGISTRATION WILL BE ON THE FOURTH FLOOR OF THE HAVANA TOWER.
It will start at 6:00 pm on Sunday December 4th and will be followed by a one-hour reception with cold drinks and snacks.
It will continue at 7:30 AM Monday December 5th through Thursday December 8th.
THREE-DAY REGISTRANTS WILL RECEIVE A BOUND COPY OF THE HANDOUTS FOR ALL SESSIONS.
RECEIPTS and a CERTIFICATE OF ATTENDANCE will be distributed at the conference. Register and pay for both the conference and the hotel online as early as possible at www.demingconference.com. This gives you an instant email acknowledgement. E-Mail Cancellations sent to registration@demingconference.com 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. Book orders can't be cancelled. If a registrant cancels, his or her ordered books would be mailed.

We are soliciting abstract proposals for posters via email to the registrar. The Poster Presentation forum, allows participants to submit their research concepts and issues of relevance for peer review in the area of biostatistics. Poster sessions, which will be held on the morning of all 3 days of the conference, allow attendees to discuss the specifics of an abstract with the author in a small group setting. Accepted poster abstracts will be published on both the website and in the transactions. Submissions will be accepted through Monday, October 31, 2016. Full details and tips for presentation, are on our website. We will hold poster sessions, providing a forum to attendees to present concepts and issues of relevance to their peers. Abstracts can be submitted online or emailed to registration@demingconference.com for consideration.

Tropicana's Havana Tower will host the Deming meeting facilities in their state-of-the-art, beachside complex with 502 nonsmoking rooms. Attendees will stay in **soundproof**, **climate-controlled** rooms with direct-dial **phones**, **cable color TV**, **coffee makers**, **hairdryers**, **refrigerators**, **safe**, **iron and board**, complimentary Wi-Fi and gorgeous views of the Atlantic City skyline. The **guest check in desk** is on the 3rd floor and meeting facilities are on the 4th floor.

The **AtlantiCare Life Center is a fully equipped fitness facility** located in the Havana Tower basement for a fee of $15/day. The **casino** is in a separate building connected by a bridge. A voucher for **free parking** and **a ticket to the holiday show** will be given to all conference registrants at registration. **Driving directions** are below. More information may be found under **MEALS** below.

TRAVEL TO THE DEMING CONFERENCE

AIR: Check both Atlantic City (ACY) and Philadelphia (PHL) to search for the best fare and connections. The cheapest quick airport connection to PHL is the Tropiano shuttle, requiring reservations at least two days in advance at (215) 616-5370. It charges $55 from PHL directly to the Tropicana. A tip is expected. There is a $10 jitney from ACY as well as a $35 taxi service to the Tropicana. For both of these, call Ext 2002 from the Taxi and Shuttle Service Desk, located in the Baggage Claim Area, near the Exit door. You can also call 609-344-8642 or 609-576-2776 in advance**.**

The cheapest connection from PHL is the below referenced SEPTA, but this will take more than two hours. One can rent a car (www.bnm.com) but it isn't necessary during one's stay. Also consider discount airlines not on the major search engines such as Spirit, www.spiritair.com (which is the only airline serving ACY); AirTran www.airtran.com, Frontier www.frontierairlines.com, and Southwest, www.southwest.com. These airlines offer the additional advantage that they sell one-way tickets without a premium that is useful if one is using the conference as a stopover.

While we don't recommend Newark Airport except as a means of saving money and perhaps travel time on international flights, there is a #67 NJ Transit bus (requiring a change at Toms River) as well as several train service options to Atlantic City, including the one referenced below. This trip would take about three hours as opposed to about ninety minutes if one rented a car.

RAIL: NJ Transit has relatively frequent local (14 daily trips with 6 stops) service to Philadelphia connecting with Amtrak, NJ Transit to NYC, and SEPTA at 30th Street and PATCO at Lindenwold. Free shuttle busses meet all trains and provide direct service to the Tropicana. www.njtransit.com/pdf/rail/R0090.pdf has a schedule that also shows the SEPTA connections from PHL to 30th Street. Direct service from NYC with a stop in Newark is available www.acestrain.com, Friday through Sunday only.

BUS: Call the Tropicana casino bus transportation department, (888) 275-1212 # 1 to find if there is service from your local neighborhood as some of these buses travel as far as 200 miles. Most allow you to return on a different day for a charge or a space available basis. Cost of the trip will be offset by casino cash back rebates and other offers. One may take a bus to any casino, collect their coins and coupons and use a $2.25 jitney on Pacific Avenue to quickly get to the Tropicana. Explore Greyhound, which has open return service with a slot play bonus from 13 cities www.luckystreakbus.com. While it has fewer trips, travel is easier than with the train as there are no transfers.

DRIVING: To get to the Tropicana from the Garden State Parkway, NJ Turnpike or Philadelphia, take the Atlantic City Expressway. Follow the Atlantic City Expressway to Exit 2. This will take you to the Black Horse Pike, Route 40/322, which you will take into Atlantic City. Turn left on Arctic Avenue, the first light over the bridge. Take Arctic Avenue to Brighton Avenue. Turn right on Brighton and cross Atlantic Avenue. The entrance to "The Quarter" Garage (Havana Tower) is on your left, off Atlantic Avenue. Valet parking doesn't permit easy access to your car during your stay so self is recommended. Don't park in the Tropicana's other garage, as it is tedious to get to the Havana Tower.

INFO: For general tourist info visit www.visitnj.org/city/atlantic-city that has an option for you to request a free visitor packet as well as an opportunity to e-mail questions that are promptly answered. Consider walking to and shopping in the upscale Atlantic City Outlets at the foot of the Atlantic City Expressway or strolling on the Boardwalk to the pier shops at Caesars. Remember there is no sales tax on apparel in NJ.

MEALS: Take the time to explore www.tropicana.net. It contains complete details of the meeting facility and gives descriptions of the 22 restaurants and other attractions. We provide a full hot breakfast on Monday and a continental breakfast on Tuesday and Wednesday before our morning sessions as well as afternoon refreshment breaks. There is a subsidized Speaker Dinner on Monday and a free one-hour reception on Sunday with cold drinks and snacks where you can meet with fellow attendees.

WALTER YOUNG SCHOLARSHIP: The ASQ Metropolitan Section will award one $4,000 college scholarship to an undergraduate spouse, child, stepchild, or grandchild of a registrant. The application, complete rules, and background information are on the conference website. The application must be submitted after the conference and before April 1, 2017. The award will be announced and paid directly to the applicant on May 15, 2017. The applicant must be accepted or matriculated at an accredited college or university in the United States and have at least a 2.75 grade point average. The Scholarship Committee, whose decision is final, reserves the right to distribute the amount of the scholarship to multiple recipients at their discretion.

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*** Walter R. Young has chaired the Deming Conference for forty-seven consecutive years.**

**** Wenjin Wang is also Webmaster & Bibliolater**

CONFERENCE SPEAKER BIOS

Jie Chen, (PhD from Temple University, MD from Fudan University), Senior Global Group Head of Biostatistical Science and Pharmacometrics, Novartis. Before joining Novartis, he held various positions in biopharmaceutical companies including nearly 15 years at Merck Research Laboratories. His experience includes clinical trial design and data analysis, statistical methodology research and applications in non-clinical, pre-clinical and clinical development, as well as safety evaluation in both clinical and post-approval settings.

Shein-Chung Chow, PhD is a Professor at the Department of Biostatistics and Bioinformatics, Duke University School of Medicine, and an adjunct at Duke-NUS, Singapore and North Carolina State University. He is also the Founding Director of the Global Clinical Trial and Research Center, Tianjin, China. Prior to joining Duke, he was the Director of the Taiwan Cooperative Oncology Group Statistical Center and the Executive Director of National Clinical Trial Network Coordination Center. He was elected an ASA Fellow in 1995 and an elected a member of the ISI (International Statistical Institute) in 1999. He was appointed as an Advisory Committee member and consultant to the FDA. He is the author or co-author of over 280 methodology papers and 24 books.

Xinping Cui, (PhD in Biostatistics from UCLA) is Professor and the Chair of the Department of Statistics at University of California, Riverside. She has been working on the development of high-dimensional data analysis and multiple testing methods with application in high-density molecular markers discovery and high throughput genotyping since 2002. She participated in many bioinformatics cooperation projects across plants, animals and humans. The NSF and the NIH have funded her research. She is co-founder of the Multiple Comparison Procedures Society, an US organization supporting international MCP conferences.

Alex Dmitrienko, (PhD in Statistics from University of Kentucky), Vice President, Mediana Inc, has over 15 years of pharmaceutical experience and has been actively involved in biostatistical research with emphasis on multiplicity issues in clinical trials, subgroup analysis, innovative trial design and clinical trial optimization. He has authored/edited two SAS® Press books (Analysis of Clinical Trials Using SAS® and Pharmaceutical Statistics Using SAS®) and a Chapman and Hall/CRC Press book (Multiple Testing Problems in Pharmaceutical Statistics). He was an Associate Editor for The American Statistician, Biometrics and Statistics in Medicine and is an ASA Fellow.

Robert Gordon received a Master in Statistics and graduate certificates in Public Health, Pharmacovigilance and Pharmacoepidemiology. He has been involved in pharmacovigilance, signal detection and data visualization. He designed and implemented end to end surveillance systems and served on the FDA/Industry/Academia Safety Graphics working group. He has been clinical trial and clinical safety statistician at J&J with a focus on immunology and process for 10 years. He is an active member of the ASA safety monitoring working group, focusing on the industry survey and regulatory guidance.

Weili He, PhD, is a Director of Clinical Biostatistics at Merck. Her research includes survival and longitudinal data modeling, missing data imputation, cancer Phase I & II designs, repeated categorical data modeling, surrogate marker evaluations, adaptive design methodologies and implementations and methods for benefit-risk assessment. She has published in the areas of adaptive designs and benefit-risk evaluations, and is the author of more than 50 peer-reviewed publications in statistical and medical journals. She served as co-chair of the QSPI Benefit-Risk and of the DIA ADSWG KOL lecture series, co-leading the DIA ADSWG Best Practice Subteam until January 2016. She is Associate Editor for the Journal of Statistics in Biopharmaceutical Research.

Richard M. Heiberger (PhD in Statistics from Harvard) is Professor Emeritus of Statistics in the Fox School at Temple University. His primary research area is statistical computing, with emphasis in statistical graphics, software design, linear models, and design of experiments. He was Graduate Chair for the Department of Statistics from 1983 to 1987 and Acting Associate Vice Provost for the University in 1989 to 1990. He has served as statistics consultant at Bell Labs and at GlaxoSmithKline. He taught short courses at the annual ASA JSMs, at the Deming Conference, and in industry. His undergraduate degree in Mathematics is from Oberlin College. He is an elected ASA Fellow and was the 2011 Chair of the ASA Section on Statistical Computing.

Qi Jiang, PhD, is an executive director of Global Biostatistical Science at Amgen, where she is therapeutic area head for oncology and hematology and leader of the Center of Excellence for Safety and Benefit-Risk. She also provides oversight to Amgen's biostatistical efforts in the Asia-Pacific region. Previously, she worked at Harvard, Merck, and Novartis. She has authored more than 60 peer-reviewed publications on method development, study design, and data analysis and reporting. She is an ASA Fellow, a co-lead of the ASA Biopharmaceutical Section Safety Working Group, a co-lead of the Quantitative Sciences in the Pharmaceutical Industry Benefit–Risk Working Group, and an associate editor for Statistics in Biopharmaceutical Research.

Judy X. Li is a Mathematical Statistician at the FDA. Her research interests include design of experiments, generalized linear mixed model/linear mixed model, longitudinal data analysis, Bayesian statistics, likelihood-based inference and simulation studies, and safety assessment of clinical trials. She is an active member of the ASA biopharmaceutical section executive committee, as the contributed poster award committee chair. She is serving as a member of the Biopharm Regulatory Statistics Workshop 2016 organizing committee and the co-lead of the ASA Safety Monitoring working group, focusing on the statistical methodology on safety monitoring.

Ilya Lipkovich, PhD, Senior Director, Quintiles, has 17 years of statistical consulting experience working in areas including econometrics, manufacturing and quality control, and pharmaceutical industry. His interests include clustering, predictive modeling and subgroup identification in clinical data using recursive partitioning, missing data and multiple imputation, and causal inference for observational data including marginal structural models and propensity-based estimation. He is a co-developer of novel subgroup identification methods (SIDES and SIDEScreen) and chairs the QSPI Subgroup Analysis Working Group.

Sandeep Menon, (MD, University of Bangalore, and PhD in Biostatistics from Boston University) is Vice President and Head of Statistical Research and Consulting Center at Pfizer and holds adjunct faculty positions at Boston and Tufts Universities. His responsibilities include providing a strong presence for Pfizer in professional circles to influence the content and interpretation of regulatory guidelines in practice. He was responsible for overseeing biostatistical aspects of more than 40 clinical trials, over 25 compounds, and 20 indications. He is a core member of the Pfizer Global Clinical Triad Leadership team.

Eva Miller, (PhD from UPenn) is Co-Chair of the DIA ADSWG BP subteam and an independent biostatistical consultant. Eva has demonstrated biostatistical leadership with over 17 years of drug development experience across all phases of clinical trials (especially Phases II-IV) in the pharmaceutical industry and CROs. Eva has extensive submission experience and experience interacting with health authorities. She has developed global, harmonized SOPs and specific quality processes and procedures for Biostatistics, and has a proven record of innovation and problem-solving and excellent knowledge of a variety of study designs and statistical methodology. Eva is particularly strong in the design and implementation of adaptive trials.

Tie-Hua Ng, (PhD in Statistics from the University of Iowa) held several positions before joining the FDA in 1987. He left the FDA in 1990 to work for the Henry M. Jackson Foundation. In 1995, he returned to the FDA, Center for Biologics Evaluation and Research (CBER). He is currently a statistical reviewer supporting the Office of Blood Research and Review within CBER. Over the past 23 years, he had made numerous presentations at professional meetings and published extensively in the area of active controlled/noninferiority studies. He offered four half-day short courses from 2009 through 2012.

William Wang, PhD, is an executive director of clinical safety and risk management in the department of Biostatistics and Research Decision Sciences (BARDS), Merck. He has more than 20 years of experience in pharmaceuticals, with expertise in statistical design, analysis and clinical data management. He has supported regulatory filings in multiple therapeutic areas and established the BARDS Asia Pacific operation. Since 2010, he has served on the DIA China Regional Advisory Board and the DIA's Global Community Leadership Council, including the chairmanship of the DIA China Statistics Community. He received the DIA global outstanding service award in 2012. He is co-leading an ASA Safety Working Group subteam and a member of the Merck benefit-risk subteam.

Bushi Wang, (PhD in Applied Statistics from UC Riverside) is a Senior Biostatistician at Boehringer Ingelheim Pharmaceuticals, Inc. since 2011. He has been working on clinical trials across different therapeutic areas and difference phases with main focus on late stage Oncology and Cardiovascular trials supporting approval. He is co-founder of the Multiple Comparison Procedures Society, an US organization supporting the international MCP conferences. He maintained a track record of statistics methodology publications as well as publications on key medical journals such as NEJM and Lancet Oncology.

Naiqing Zhao, Professor, Department of Biostatistics, School of Public Health, Fudan University, China. His experience spans from the design and analysis of clinical trials, clinical epidemiology, biological signaling, to statistical methodology research in biomedical field. He has been teaching biostatistics for over 20 years and served as an external review expert of clinical trial statistics for the China Food and Drug Administration for more than a decade. He received a Bachelor degree in mathematics from Fudan University and a Master's degree in biostatistics from the University of Newcastle, Australia.

Richard C. Zink, (PhD in Biostatistics from University of North Carolina at Chapel Hill) is Principal Research Statistician Developer in the JMP Life Sciences division at SAS® Institute, following eight years in the pharmaceutical industry, and an adjunct faculty member at Chapel Hill. He is Statistics Section Editor for Therapeutic Innovation & Regulatory Science, and Publications Officer for the Biopharmaceutical Section of the ASA. He is author of Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP and SAS®.

Monday, December 5, 2016

Morning Sessions 8:30 AM – 11:45 AM

Session A 🕮

Data Display for Statistical Analysis

Richard M. Heiberger, Temple University

Moderator: Walter R. Young

Complex data analyses may require complex graphs to place the full information of the analysis into a form that the intended client will be able to read. Data analysts are responsible for the display of data with graphs and tables that summarize and represent the data and the analysis. Graphs are often the output of data analysis that provides the best means of communication between the data analyst and the client. Gaining an understanding of a data set is always more easily accomplished by looking at appropriately drawn graphs than by examining tabular summaries.

We will look at many examples of graphs, from simple to complex. We need to begin with simple graphs to learn the vocabulary of graphs. We then proceed to more complex graphs and see how they are constructed by using the same graphic vocabulary. We discuss the principles of good graphs and show why they are important for communication between the data analyst and the client. Topics include: the design of multi-panel graphics; graphing Likert Scale Data to build on the importance of rating scales; the design of graphics that will work for readers with color-deficient vision; and interactive graphs. Most of the examples will be from the medical/pharmaceutical areas or from social sciences. The concepts are much more broadly applicable.

Session B 🕮

Noninferiority Testing in Clinical Trials: Issues and Challenges

Tie-Hua Ng, Food and Drug Administration

Moderator: Wenjin Wang

The objective of a noninferiority (NI) trial is to show that the test treatment or the experimental treatment is not inferior to the standard therapy or the active control by a small margin known as the NI margin. This tutorial elaborates the rationale of choosing the NI margin as a small fraction of the therapeutic effect of the active control as compared to placebo in testing of the NI hypothesis of the mean difference with a continuous outcome. This NI margin is closely related to M_1 and M_2, the NI margins discussed in the FDA draft guidance on NI clinical trials issued in March of 2010.

This tutorial also covers fundamental concepts related to NI trials, such as assay sensitivity, constancy assumption, discounting and preservation. As time permits, this tutorial (i) explains the differences between fixed-margin and synthesis methods, (ii) addresses the issues of switching between superiority and noninferiority, (iii) discusses gold-standard design and the equivalency of three or more treatment groups, (iv) investigates the roles of intention-to-treat and per-protocol analyses, and (v) presents an extended example of thrombolytic therapies.

Afternoon Sessions 1:30 PM - 4:30 PM

Session C🕮

Overview of Statistical & Design Considerations in Personalized Medicine

Sandeep Menon, Pfizer

Richard Zink, JMP Life Sciences, SAS® Institute

Moderator: Kalyan Ghosh

Personalized medicine is described as providing "the right patient with the right drug at the right dose at the right time for the right outcome." Personalized medicine is a relatively young but rapidly evolving field of clinical research. It involves identifying genetic, genomic, and clinical characteristics that have the potential to accurately predict patient's susceptibility of developing a certain disease and its response to treatment. Personalized medicine is the translation of this knowledge to patient care. However, this "translation" can be very challenging in the phase of limited knowledge of the biomarker and /or appropriate diagnostics. Hence, the appropriate selection of the study design is important to critically determine biomarker performance, reliability and eventually regulatory acceptance.

In 2012, FDA released a draft guidance on enrichment strategies for clinical trials to support approval of human drugs and biological products. In their guidance, the term enrichment is defined as “the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population”. This tutorial will provide a general overview of the concept and statistical methodology related to personalized medicine. Specifically, it will discuss various population enrichment designs including adaptive designs available at our disposal and its merits and limitations. Case studies will also be presented.

Session D 🕮

Benefit–Risk Assessment Methods in Medical Product Development: Bridging Qualitative and Quantitative Assessments

Qi Jiang, Amgen and **Weili He**, Merck

Moderator: Alfred H. Balch

Evaluation of a new treatment has always required a benefit-risk (B-R) assessment. However, in the past the assessment tended to be informal and was often subjective, involving judgments from separate assessments of efficacy and safety. Notably, a few regulatory submissions in the last few years failed to gain regulatory approval due to benefits that did not outweigh risks. Such failures speak to the importance of structured B-R assessments to improve consistency, transparency, communication, and objectivity. However, B-R assessment is multi-faceted and complex, and the B-R landscape is still evolving. There is increased interest and effort from companies, regulatory agencies, and other governance bodies to further enhance structured B-R assessments. Amid numerous existing frameworks, metrics, estimation techniques, and utility survey techniques in B-R assessment, however, there is still no commonly accepted B-R approach. Guidance on how to select specific B-R frameworks and quantitative methods, along with case studies and best practice sharing, is still lacking.

This tutorial provides general guidance and case studies to aid statisticians in selecting specific benefit–risk frameworks and quantitative methods. We will present practical examples, lessons learned, and best practices that illustrate how to conduct structured B–R assessment in clinical development and regulatory submission. The first part of the tutorial covers the role of B–R assessments in medicine development and regulation, along with key elements of B–R evaluations in a product’s life cycle. The second part presents visual tools for B-R evaluations along with a couple of illustrative case studies for lessons learned and best practice sharing.

7:00 PM Speaker’s Dinner (Optional Added Fee Event)

Tuesday, December 6, 2016

Morning Sessions 8:30 AM – 11:45 AM

Session E
Biomarker Evaluation and Subgroup Discovery in Clinical Trials

Ilya Lipkovich, Quintiles and **Alex Dmitrienko**, Mediana Inc
Moderator: Kalyan Ghosh

This half-day course focuses on a broad class of statistical problems arising in the development of personalized medicine/tailored therapeutics. Vast literature has been generated in medical and statistical journals over the last 15 years concerning identification of biomarker-based patient subgroups and assessment of their validity/credibility. Principled analytical approaches have been replacing ad-hoc approaches and this half-day course will present a survey of recently developed methods aimed at identifying predictive biomarkers and subgroups with desirable characteristics (e.g., enhanced efficacy). These methods can be utilized in Phase II clinical trials to select promising biomarkers for later stages of drug development (e.g., for Phase III enrichment trials) or for rescuing failed Phase III trials.

Commonly used approaches to biomarker evaluation and subgroup identification in the context of personalized medicine will be introduced. This introductory module will be followed by a detailed discussion of the SIDES method (Subgroup Identification based on Differential Effect Search) introduced in Lipkovich et al. (2011). SIDES is based on recursive partitioning and can be used in prospective and retrospective analysis. Key elements of SIDES will be discussed, including generation of multiple promising subgroups based on different splitting criteria, complexity control to reduce the size of the search space and resampling-based approach to controlling the Type I error rate. In addition, efficient two-stage SIDEScreen procedures (Lipkovich and Dmitrienko, 2014a) that compute variable importance scores to pre-screen candidate biomarkers will be introduced.

Multiple case studies will be used to illustrate the principles and statistical methods introduced in this course, including design and analysis of Phase III trials with target subgroups and biomarker discovery in Phase III development programs (Lipkovich and Dmitrienko, 2014b; Dmitrienko et al., 2015). Software tools for implementing the biomarker and subgroup analysis methods in clinical trials will be presented, including the R package developed by the authors and Windows application.

Session F
Basic Multiple Comparisons in Clinical Trials and Genomics

Bushi Wang, Boehringer Ingelheim
Xinping Cui, University of California, Riverside
Moderator: Naitee Ting

Multiple comparison is a very common practice in pharmaceutical and biotech industries. Traditional clinical trials with multiple endpoints and multiple doses require the use of multiple comparison procedures to protect the familywise error rate. Recently the advance of personalized medicine requires the use of biomarkers to identify patient subgroups and multiplicity issues raise in these studies demand careful selection of multiple comparison procedures. There are abundant literatures in the field of multiple comparisons since the 70's and more advanced techniques are developed rapidly in the past decade.

In this presentation, we would provide an opportunity to survey some early publications as well as highlight of some recent advancement in multiple comparison procedures with applications to clinical trials and genomic. Audience of the presentation can expect to be refreshed with the most commonly used multiple comparison procedures, closed testing and newer concept such as partition testing, graphical approach and gatekeeping. We will discuss methods for family-wise error control, false discovery rate control, local false discovery rate control and false discovery proportion estimation in genomic data analysis.

We will also examine critically the interpretation and implication of controlling these error rates for discovery of potential biomarkers and explain when to use which type of error rates.

Afternoon Sessions 1:30 PM - 4:30 PM

Session G
Quantitative Sciences for Safety Monitoring in Clinical Development

Bill Wang, Merck, **Robert Gordon**, JNJ and **Judy Li**, FDA
Moderator: Ivan S. F. Chan

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.

We conclude with a panel discussion. Dr Qi Jiang (Executive Director, Global Biostatistical Science, Amgen) and Dr Olga Marchenko (Vice President, Head of Quintiles Advisory Services Analytics), who established and co-lead the ASA safety working group, will join the 3 speakers in the panel discussion. We will expand our discussion from safety monitoring to regulatory submission and safety confirmation trials (either as pre-marketing or post-marketing commitments). Audience participation will be highly encouraged.

Session H
Improving Our Understanding of "Less Well-Understood" Adaptive Trials: Challenges, Best Practices & Sharing of Case Studies

Weili He, Merck and **Eva Miller**, Independent Consultant
Moderator: Xiaoming Li

The draft adaptive design guidance released by FDA in 2010 included references to adaptive study designs that were described as "less well-understood". There was relatively little regulatory experience with such designs and their properties were felt not to be adequately understood at the time of draft guidance release. In order to promote greater use of adaptive designs, especially those that were categorized as less well-understood, the Best Practice Subteam of the DIA Adaptive Designs Scientific Working Group has worked on describing and characterizing these designs, identifying challenges associated with them, and making suggestions on design or study conduct improvements that could make them more acceptable.

In addition, the Best Practices Subteam conducted an extensive anecdotal search and reviewed trials from multiple sponsors who had employed these designs. We learned that these "less well understood" AD designs and associated statistical design and analysis methodologies can make difficult research situations more amenable to research, and, therefore are needed in our toolbox. This tutorial will cover the following two main parts: In the first part we will describe challenges of the "less well-understood" trials and suggest possible improvements to study design and/or study conduct; in the second part we will describe a few case studies in greater detail to give a more complete picture of lessons learned and best practices.

Wednesday, December 7, 2016

Morning Sessions 8:30 AM – 11:45 AM

Session I
Simulation-Based Approaches to Clinical Trial Design & Analysis

Alex Dmitrienko, Mediana Inc
Moderator: Kalyan Ghosh

This half-day course focuses on a broad class of statistical problems related to simulation-based assessment of optimal trial designs and analysis strategies in Phase II and III trials (Dmitrienko and Pulkstenis, 2017). This general topic has attracted much attention across the clinical trial community due to increasing pressure to reduce implementation costs and shorten timelines. The Clinical Scenario Evaluation (CSE) framework (Benda et al., 2010) will be described in this short course to formulate a general approach to optimal decision making in clinical trials. The CSE framework facilitates a comprehensive comparison of competing options for clinical development programs and clinical trial designs/analyses. The concept includes three different elements, namely, the set of underlying assumptions (data models), the options to be assessed (analysis models) and the metrics used for the assessment (evaluation models).

A comprehensive assessment of candidate designs and analysis methods makes heavy use of clinical trial simulations. Simulation-based approaches to evaluating trial designs and analysis methods will be discussed based on the general CSE approach. Simulation-based approaches will be illustrated using a number of problems that often arise in Phase II and III clinical trials. This includes optimal selection of analysis strategies that involve multiplicity adjustments (Dmitrienko et al., 2009; Dmitrienko, D'Agostino and Huque, 2013), selection of design elements in adaptive clinical trials (Dmitrienko et al., 2016) and selection of patient subgroups in enrichment designs. Practical solutions that the participants can quickly apply to address real-life challenges in clinical trials will be emphasized throughout this short course.

Multiple case studies based on real Phase II and III trials will be used, e.g., clinical trials with multiple endpoints and dose-placebo comparisons, trials with adaptive and enrichment designs. Software tools for applying the simulation-based CSE approaches will be presented, including R software (Mediana package) and Windows application with a graphical user interface (MedianaPro application).

Session J
Statistical Considerations for Drug Development in China: Recent Development and Future Directions

Naiqing Zhao, Fudan University and **Jie Chen,** Novartis
Moderator: Xiaoming Li

As one of the world's largest pharmaceutical markets, China has enjoyed in the past decade or so a double-digit annual growth rate in pharmaceutical revenue. According to China's National Development and Reform Commission, the country's pharmaceutical sales grew 17.9% in 2013 over the year before. The trend of robust growth is expected to continue perceivably due to the combined forces of rapid economic development, increasing medical care reimbursement coverage by the government, enhanced health care awareness, and huge, yet still growing, aging population with vast unmet medical needs.

Along with the immense market potential and strong demand of innovative products, pharmaceutical development activities including clinical trials and subsequent application for new drug registrations have posed a substantial increase in recent years. For instance, the number of applications for Investigational New Drugs (IND) including multi-regional clinical trials (MRCT) received by the Center for Drug Evaluation (CDE) of the China Food and Drug Administration (CFDA) rose from 267 in 2012 to 382 in 2013, representing a 43% increase, and the number of clinical trials for imported drugs (so called "validation clinical trials") received by the same agency rose from 787 in 2012 to 1173 in 2013, a jump of over 49%. Because of the evident advantages of conducting clinical trials in China (e.g., faster patient recruitment, larger treatment-naive patients, relatively lower costs, and early market entry, etc.), the number of applications for global clinical trials in the first half of 2013 is nearly equal to that for 2011 and 2012 combined.

This tutorial will include discussions on the following

(1) Introduction to the statistical guidance for clinical trials (revised);
(2) Guideline for multi-regional clinical trials;
(3) Provisions for drug registration (revised);
(4) Data standards for clinical trials;
(5) General considerations for clinical trial applications;
(6) General considerations for new drug registration;

Through the tutorial, the audience is expected to learn the statistical considerations in the design, analysis and data interpretation of clinical trials and new drug registrations. Special considerations will also be discussed for rare diseases (e.g., multiple sclerosis), China prevalent diseases (e.g., esophageal cancer, liver cancer, COPD, etc.) with respect to trial design and analysis, as well as registration requirements by CFDA.

Afternoon Sessions 1:30 PM - 4:30 PM

Session K
Regulatory Statistics With Some European Perspectives

Martin Posch & **Franz Köenig** (Medical University of Vienna)
Frank Bretz (Novartis)
Moderator: Ivan S. F. Chan

We start with an overview of the European regulatory system, explaining the main regulatory bodies (EMA, national agencies) and their working parties (CHMP, SAWP, PDCO, COMP, BSWP, MSWP, ...). We also discuss regulatory procedures in Europe (such as scientific advice and protocol assistance) and the concept of seeking for qualification opinions of novel methodologies for medicine development. We illustrate these procedures with a review on scientific advice letters on adaptive designs and with the recent MCP-Mod qualification opinion, which marks the first, and to date the only clinical trial methodology formally endorsed by any regulatory agency. This discussion leads into an overview of European statistical guidance documents (Concept Papers, Reflection Papers, ...) on statistical topics that have recently been published or are current under discussion. We complement the overview of the European regulatory system with an overview of the European industry associations and initiatives (EFPIA, EFSPI, PSI, IMI, ...). Finally, we conclude this tutorial with a discussion of two scientific topics that are currently receiving considerable attention in Europe: the addendum to the ICH E9 guidance on choosing appropriate estimands and defining sensitivity analyses in clinical trials and data sharing and publication of clinical trial data.

Session L 🕮
Quantitative Methods for Traditional Chinese Medicine Development

Shein-Chung Chow, Duke University School of Medicine
Moderator: Naitee Ting

In recent years, the use of complementary and alternative medicine including botanical drug product and traditional Chinese (herbal) medicine (TCM) in humans for treating critical and/or life-threatening diseases has received much attention. In pharmaceutical/clinical development of a given TCM, one of the major criticisms is lack of objectively scientific evidence (documents) of clinical safety and efficacy. Unlike the Western medicines (WM), TCM often consists of multiple components (active ingredients) whose pharmacological activities are often unknown or are not fully characterized or understood. Thus, standard methods for WM clinical trials may not be appropriately applied directly to TCM clinical trials. This tutorial discusses some statistical considerations including the selection of study design, preparation of matching placebos, development of study endpoints, validation of an instrument, calibration of the validated instrument and power calculations for sample size estimation. These considerations have an impact on effectively and scientifically evaluation of clinical safety and efficacy of TCM in clinical trials. In addition, some practical issues regarding test for consistency in raw materials, stability of drug substance, and animal studies are also discussed.

TWO SIMULTANEOUS SHORT COURSES THURSDAY AND FRIDAY, DECEMBER 8-9, 2016

Registration includes (1) a **hot breakfast** and **two refreshment breaks each day**; (2) **handouts** and (3) **the text**. **No registrations will be accepted without payment in full**. *We will refund full tuition if courses are canceled due to insufficient registration.*

8:00–9:30: Lecture / 9:30–9:50: *Break* **/ 9:50–11:20: Lecture / 11:20–12:40:** *Lunch* **/ 12:40–2:10: Lecture / 2:10–2:30:** *Break* **/ 2:30–4:00: Lecture / 4:00-4:20:** *Break* **/ 4:20-5:50: Lecture**

There will be five lectures on Thursday and three on Friday to allow attendees time to catch their flights.

Adaptive Designs and Multiple Testing 🕮

Martin Posch & **Franz Köenig**, Medical University of Vienna
Frank Bretz, Novartis
Moderator: Ivan S. F. Chan

Text: Group Sequential & Confirmatory Adaptive Designs in Clinical Trials*

This course gives an introduction to multiple testing, adaptive design and dose finding methodology and its application in clinical trials. We cover common multiple testing problems including the comparison of several doses with a control, assessing the benefit of a new treatment for more than one endpoint, testing of subgroups, combined non-inferiority and superiority testing, or any combination thereof. Besides more traditional approaches, we introduce graphical methods and show how to construct multiple testing procedures that reflect the often complex contextual relations between hypotheses in clinical trials.

In addition to fixed sample tests, we give an introduction to the key principles and statistical methodologies of adaptive designs for clinical trials. Adaptive (flexible) designs allow for mid-course design adaptations based on interim data without compromising the overall type I error rate. Examples of design adaptations are the adjustment of sample sizes or the number and timing of interim analyses. These design parameters may be adapted depending on interim estimates of the variance, the treatment effect and safety parameters. An important field of application of the adaptive design methodology is clinical trials with several treatment arms, where promising treatments can be selected at an interim analysis. Using adaptive multiple test procedures the type I error rate can be controlled even if the selection rule, the number of selected treatments or the final sample sizes are not prefixed. Adaptive multiple testing procedures can also be used in adaptive designs with the option of population enrichment. In such designs a sub population may be selected in an interim analysis and further recruitment of patients is restricted to the selected subgroup.

Another application arises in dose finding studies, where multiplicity due to model uncertainty has to be addressed, e.g. by using MCP-Mod. Finally, we show how the toolbox of multiple testing, adaptive designs and dose finding methodology can be combined to design confirmatory phase II/III trials and several case studies will be discussed.

Day 1 of the course will cover:

- Introduction to multiple testing
- Multiple Comparison Procedures (MCP): from Bonferroni to closed testing
- Graphical approaches to multiple testing
- Group sequential designs
- Adaptive combination tests and multiple testing in adaptive designs

Day 2 of the course will cover:

- Introduction to exploratory and confirmatory dose finding
- MCP-Mod, Confirmatory MCP-Mod and Adaptive MCP-Mod
- Adaptive Graph Based Methods
- Regulatory and practical experience with innovative trial designs

Franz Köenig is Associate Professor at the Section of Medical Statistics at the Medical University of Vienna, Austria. He regularly serves as member of ethics committees and DSMBs. From 2008 till 2010 he was seconded to the European Medicines Agency as statistical expert. His main research interests are multiple testing and adaptive designs.
See www.meduniwien.ac.at/user/franz.koenig .

Martin Posch is professor of Medical Statistics at the Medical University of Vienna, Austria, and head of the Center for Medical Statistics, Informatics and Intelligent Systems. From 2011-2012 he worked as statistical expert at the European Medicines Agency. His research interests are group sequential trials, adaptive designs and multiple testing.
See www.meduniwien.ac.at/user/martin.posch .

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. He is an Adjunct Professor at the Hannover Medical School, the Shanghai University of Finance and Economics and the Medical University of Vienna.

** The textbook covers similar material but the course is not based on it.*

Bioequivalence, Biosimilars & Statistics in Clinical Pharmacology 🕮

Scott Patterson, Pfizer; **Byron Jones** & **Johanna Mielke**, Novartis
Moderator: Alfred H. Balch

Text: Bioequivalence and Statistics in Clinical Pharmacology, 2ed.

This course will cover the application and basic elements of the theory of statistical methods in clinical pharmacology. The course will first concentrate upon the techniques used in the assessment of bioequivalence - the study of a drug formulation to confirm its equivalence to another.

The second day will cover newer approaches, scaled average bioequivalence and the developing field of biosimilars, and will touch upon the use of statistics in clinical pharmacology studies of safety and lot consistency studies in Vaccines. The emphasis will be on study design, analysis, and interpretation of data using real-data examples from the authors' experiences.

The course will provide attendees with: (1) a wide range of real examples with datasets, SAS® and R code (from the website accompanying the textbook), (2) applications of statistics in clinical pharmacology drug development with an emphasis upon regulatory applications, and (3) a detailed consideration of the statistical analysis and design of bioequivalence, biosimilarity, and clinical pharmacology studies.

Day 1 of the course will cover:

- Biopharmaceutical Development and Clinical Pharmacology (Scott)
- History and Regulation of Bioequivalence (Scott)
- Testing for Average Bioequivalence (Byron)
- Sample size re-estimation in Average Bioequivalence studies (Byron)

Day 2 of the course will cover:

- Scaled Average Bioequivalence (Scott)
- Biosimilarity (Johanna)
- Lot Consistency Studies in Vaccines (Scott)
- Clinical Pharmacology Safety Studies (Byron)

The addition of the section on biosimilarity represents significant new material since the first (and second) approvals of biosimilar products. Biosimilars are biologics that are highly similar to an approved reference product which are shown not to differ meaningfully in safety and efficacy from the approved product.

Scott Patterson, PhD, PStat® is currently the Senior Director of Vaccines Clinical Biostatistics and Quantitative Modelling at Pfizer. He is an expert on the design and statistical analysis of clinical and clinical pharmacology trials and has over 20 years of statistical consulting and collaborative experience.

Byron Jones, PhD, PStat® is a Senior Biometrical Fellow and Executive Director at Novartis Pharma AG. He is an expert in the design and statistical analysis of cross-over trials and co-authored the classic text on this topic (now in its third edition), in addition to his book on Statistical Inference and the textbook used in this course. He is an ASA Fellow and has over 30 years of statistical consulting and collaborative experience.

Johanna Mielke, MSc, received her Master's Degree in Statistics from the TU Dortmund University in 2015. She is working as a Doctoral Candidate at Novartis Pharma AG. The research for her PhD thesis focuses on optimal designs and analysis methods for the development and approval of biosimilars.

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For Conference Tutorials, December 5-9	**Payment must be made or check must be mailed on or before**				
	October 1	November 1	December 1	Later or Onsite	Total
Three Days Conference	$670 ❑	$800 ❑	$850 ❑	$1050 ❑	
One Day Conference (Mon, Tues, or Wed)	$325 ❑	$380 ❑	$430 ❑	$510 ❑	
Retiree/Student (Proof of status needed)	$275 ❑	$325 ❑	$375 ❑	$475 ❑	
Speakers Dinner (Optional, Monday 7:00 pm)	$50 ❑	$60 ❑	$60 ❑	$60 ❑	

Bound proceedings, which include handouts for all tutorials, will be provided to all attendees.

Registration for a short course is **required and independent** of the registration for the tutorial sessions. The registration fee covers the textbook used in the short course. Onsite short course registration requires advance e-mail or telephone notification so we can guarantee sufficient materials.

For Short Courses, December 8-9	**Payment must be made or check mailed on or before**				
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Adaptive Designs and Multiple Testing	$910 ❑	$1030 ❑	$1,080 ❑	$1150 ❑	
Bioequivalence, Biosimilars and Statistics in Clinical Pharmacology	$910 ❑	$1030 ❑	$1,080 ❑	$1150 ❑	

Book Title, Author(s) / (Sessions/Course titles marked with 🕮 have a textbook below) Onsite availability of books cannot be guaranteed unless you place an order in advance	# of Pages	Year	ISBN 13-978	Price ($) List	Price ($) Our	# of Copies	Total ($)
CHAPMAN AND HALL/CRC							
Noninferiority Testing in Clinical Trials: Issues and Challenges, Tie-Hua Ng	208	2014	1466561496	~~80~~	**51**		
Benefit-Risk Assessment Methods in Medical Product Development: Bridging Qualitative and Quantitative Assessments, Qi Jiang, Weili He	296	2016	1482259360	~~100~~	**63**		
Quantitative Methods for Traditional Chinese Medicine Development, Shein-Chung Chow	430	2015	1482235999	~~120~~	**75**		
Bioequivalence and Statistics in Clinical Pharmacology, Scott D. Patterson, Byron Jones, 2nd ed.	480	2016	1466585201	~~120~~	**75**		
SPRINGER							
Statistical Analysis and Data Display - An Intermediate Course with Examples in R, Heiberger, Richard M., Holland, Burt, 2nd ed.	898	2015	1493921218	~~80~~	**52**		
Group Sequential and Confirmatory Adaptive Designs in Clinical Trials, Gernot Wassmer, Werner Brannath	303	2016	3319325606	~~129~~	**80**		
SAS® INSTITUTE							
Modern Approaches to Clinical Trials Using SAS®: Classical, Adaptive, and Bayesian Methods, Sandeep Menon, Richard C. Zink	364	2015	162959385	~~70~~	**45**		

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