PROGRAMME OF THE SIXTY-SEVENTH ANNUAL DEMING CONFERENCE ON APPLIED STATISTICS

Sponsored by
AMERICAN SOCIETY FOR QUALITY
NY/NJ Metropolitan Section ~ ~ Statistics Division
AMERICAN STATISTICAL ASSOCIATION: Biopharmaceutical Section
December 5 – December 7, 2011: Three-Day Conference
Tropicana Casino and Resort, Havana Tower, Atlantic City, NJ

Short Courses: – December 8-9, 2011

1. **Modeling Survival Data: Extending the Cox Model by Terry M. Therneau, PhD, Mayo Clinic**
2. **Novel Approaches To Multiple Test Problems, With Applications To Adaptive Designs by Frank Bretz, Willi Maurer, & Jeff Maca, 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 Wednesday December 7th and 8 AM Thursday December 8th.
ALL REGISTRANTS WILL RECEIVE A BOUND COPY OF THE AVAILABLE HANDOUTS FOR ALL SESSIONS.
Please register for both the conference and the Tropicana online at www.demingconference.com. This will give you an instant e-mail acknowledgement. Pay online with a credit card or mail a check for the amount of your bill in your acknowledgement. If checks are not postmarked on or before the early discounted registration date, you will be charged the next higher amount.

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The conference will use the meeting facilities in the Tropicana's Havana Tower state-of-the-art complex with 502 nonsmoking rooms where attendees stay in soundproof climate controlled rooms with direct-dial phones, cable color TV, coffee makers, hairdryers, refrigerators, complimentary wireless internet and gorgeous views of the Atlantic City skyline. Use the Havana Tower parking garage (the sign says "The Quarter") on Brighton Avenue. Self-parking or valet (for hotel guests) is $5 per stay. Guests not requiring overnight accommodations are subject to either a $5 self-parking or a $10 valet fee.

- There is a guest check in desk on the 3rd floor of the Havana Tower and all meeting facilities are on the 4th floor.
- It is the largest hotel in New Jersey, with 2,125 rooms, elegant public areas, exclusive retail shops and fine dining.
- It is on the beach with a fully equipped fitness facility (free for conference registrants) and a heated indoor pool.
- Wireless for registrants is free on the conference floor. The casino is in a distant, separate connected building.
- A free Diamond Club Card can offer rewards based on your play and may offer dining and show discounts.

Joseph C. Cappelleri (PhD in psychometrics from Cornell University) joined Pfizer in 1996 as a Biostatistician collaborating with Outcomes Research and is now a Senior Director. He is also an adjunct professor of medicine at Tufts Medical Center and an adjunct professor of statistics at the University of Connecticut. He has published extensively on clinical and methodological clinical topics, including on regression-discontinuity designs, meta-analyses, and health measurement scales. He has been instrumental in developing and validating a number of patient-reported outcomes for different diseases and conditions. He is an ASA Fellow.

Ding-Geng (Din) Chen (PhD in Statistics from University of Guelph) is a professor in biostatistics at the University of Rochester Medical Center. Previously, he was the Karl E. Peace endowed eminent scholar chair in biostatistics from the Jiann-Ping Hsu College of Public Health at the Georgia Southern University. He is also a senior biostatistics consultant for biopharmaceuticals and government agencies with extensive expertise in clinical trials and bioinformatics. He has more than 80 refereed professional publications and co-authored two of the books in our book list with Professor Karl E. Peace.

Michael. Chernick (PhD in statistics from Stanford University) worked his entire career in industry but has also done part-time teaching and currently teaches an online course on the bootstrap at statistics.com. He is a Fellow of the ASA, a member of the International Biometrics Society, the Royal Statistical Society, the Institute of Mathematical Statistics, and the Bernoulli Society. For the last 15 years he has worked on clinical trials for medical device and pharmaceutical companies. At the Lankenau Institute for Medical Research, he provides statistical support for clinical trials in oncology, cardiology and electrophysiology as well as providing input to grant proposals to the Sharpe-Strumia Foundation and the NIH in support of advanced research methods with animal models and molecules.

Susan S. Ellenberg (PhD in Mathematical Statistics from the George Washington University) is Professor of Biostatistics, Center for Clinical Epidemiology and Biostatistics, and Associate Dean for Clinical Research, University of Pennsylvania School of Medicine. She is a Fellow of the ASA, the Society for Clinical Trials and the American Association for the Advancement of Science, and is an elected member of the International Statistical Institute. Her co-authored book on data monitoring committees was named Wiley Europe Statistics Book of the Year for 2002. As Associate Dean, she oversees the human subjects protections programs.

David A. Evans is a senior technology and clinical research executive with over thirty years experience in the clinical research, regulatory and healthcare industries. He has served as Chief Technology and Information Officer for leading clinical research organizations and as Chief Operating Officer for several clinical software development firms. He has extraordinary experience in corporate development, clinical data management, clinical trial management, complex clinical data warehousing, regulatory data analysis, automated data capture and clinical business process engineering. He was the architect and developer of the first electronic submission to the FDA in 1985 and has been responsible for numerous electronic submissions over the past 25 years. He currently serves as Chief Information Officer for Octagon Research Solutions.

Michael D. Hale (PhD in Mathematical Statistics from Iowa State University) is Executive Director Medical Sciences Biostatistics, Amgen, with responsibility for statistics for Research and Translational Sciences. In the early 1990's he proposed and developed the current paradigm of clinical trial simulation using models relating dosing, pharmacokinetics, and clinical response including stochastic components. These methods were used to enable a Randomized Concentration Controlled Trial (RCCT) for mycophenolate mofetil (Cellcept®) for renal transplantation. He has served as a member of the Clinical Pharmacology sub-team of the FDA Pharmaceutical Sciences Advisory Committee. Recent talks have focused on adaptive trial design and the use of biomarkers in drug development.

M. Elizabeth Halloran (MD from the Freie Universitaet, Berlin) is a Professor of Biostatistics at the University of Washington and the Fred Hutchinson Cancer Research Center. Her main research interests are in developing novel designs, methods of statistical analysis, and interpretation of vaccine field studies and other interventions, and in causal inference. Her novel study designs and statistical methods have been used in studies of pertussis, malaria, and influenza, among others. She has contributed extensively to dynamic transmission models, including influenza, malaria, chickenpox and tuberculosis. She is Associate Editor of Biometrics, and on the Editorial Boards of Statistical Communications in Infectious Diseases and Epidemics. She is founder and Director of the Summer Institute of Statistics and Modeling in Infectious Diseases at the University of Washington. She is a Fellow of the American Association for the Advancement of Science, the ASA and the Royal Statistical Society.

Jeffrey Harring (PhD in Quantitative Methods Program within Educational Psychology from University of Minnesota) is Assistant Professor in the Department of Measurement, Statistics, and Evaluation at the University of Maryland. He currently focuses his research on statistical models for repeated measures data and nonlinear structural equation models.

H. M. James Hung, PhD, is Director of Division of Biometrics I, CDER, FDA. This division provides services for 3 medical divisions of drug products (cardiovascular- renal, neurology, psychiatry). In his FDA tenure, he reviewed many large mortality/morbidity trials in cardiovascular-renal areas. He published in Biometrics, Statistics in Medicine, Biometrical Journal, etc. His research covers factorial trials, utility of p-value distribution, adaptive design/analysis, non-inferiority trials and multi-regional trials. He received two FDA/CDER level Scientific Achievement Awards and was recently awarded an FDA level Scientific Achievement Award in recognition of his sustained excellent achievements to regulatory science in areas of clinical trial methodology. He is a Fellow of the ASA and an elected member of the International Statistical Institute.

K. K. Gordon Lan (PhD in Mathematical Statistics from Columbia University) joined J&J in 2005 after holding positions as a Mathematical Statistician at the National Heart, Lung and Blood Institute (NHLBI/NIH), Professor of Statistics at George Washington University, Distinguished Scientist at Pfizer and Statistics Fellow at Sanofi-Aventis. He has published more than 60 research papers in professional journals, and has given more than 200 invited talks at universities and professional meetings. He is a Fellow of the ASA.

Scott D. Patterson (PhD from the University of Queensland) is an Executive Director in the Medical Sciences function at Amgen leading the Molecular Sciences department (including the Computational Biology department) since 2003. His departments are responsible for the implementation of Amgen's biomarker strategy from first-in-human studies through to companion diagnostics including the development of KRAS as a predictive biomarker for Vectibix® therapy. He has published extensively in the field of proteomics and biomarkers. His academic career encompassed work on analytical protein chemistry applications & apoptosis.

Ewout W. Steyerberg (PhD from University of Leiden) is head of the Center for Medical decision-making, Department of Public Health, Erasmus MC. He is responsible for a group of 20 academic research staff, including statisticians, epidemiologists, economists and psychologists. His research has covered a broad range of methodological and medical topics. His methodological expertise is in the design and analysis of randomized controlled trials, cost-effectiveness analysis, and decision analysis. Medical fields of application include oncology, cardiovascular disease, internal medicine and traumatic brain injury.

Sue-Jane Wang, PhD is Associate Office Director for Pharmacogenomics and Adaptive Design, Office of Biostatistics, Office of Translational Sciences, CDER, FDA. She is an author of over 90 papers and book chapters in statistical, clinical, genetic, bioinformatics, and pharmacogenomics literature. She received two FDA Outstanding Intercenter Scientific Collaboration Awards and was recently awarded the FDA level Scientific Achievement individual Awards in recognition of her sustained record of published regulatory research in statistical design and methodology advancing complex and emerging clinical trial designs and analysis that support regulatory guidance, policies and review in 2010. She is an ASA Fellow and an elected member of the International Statistical Institute.

Kathleen W. Wyrwich (PhD in Health Services Research from Saint Louis University) is a Senior Research Leader at United BioSource Corporation. She has over 15 years experience in designing and conducting studies involving health-related quality of life assessment, evaluation, health services research, psychometrics, heterogeneity analyses and primary care research. Her primary research interest is in the development and application of methodologies to study change in health outcomes and the determination of relevant thresholds that identify important changes over time. She has designed and conducted patient-reported outcomes studies in many areas, including cardiovascular and respiratory diseases, Alzheimer's disease, mental health, women's health, pain and oncology.

Andrew Zieffler (PhD from University of Minnesota) is Lecturer in the Department of Educational Psychology at the University of Minnesota. He has published numerous articles in his areas of research interest, which include the measurement and assessment in statistics education research and statistical computing.

Monday December 5, 2011 8:30 – 11:30 AM

Session A 🕮
Data Monitoring Committees: Areas of Consensus & Controversy
Prof Susan S. Ellenberg, University of Pennsylvania
Moderator: Kalyan Ghosh

Data Monitoring Committees (DMCs), also known as Data and Safety Monitoring Boards (DSMBs), are often established as a component of clinical trial oversight to review interim data of the ongoing trial so that safety concerns or problematic operational issues can be identified rapidly and corrective measures undertaken. Such committees may be independent of the trial sponsor and investigator to ensure recommendations are as objective as possible and unaffected by conflicts of interest. Funding and regulatory agencies in the U.S. and elsewhere have issued policy documents concerning the establishment and operation of DMCs, but substantial variation remains in operational procedures and debates have arisen regarding "best practices," even within a single agency such as the NIH. Areas of general consensus include the need for a committee charter, the value of "open" and "closed" sessions, allowing opportunities for the DMC to interact with sponsor representatives; the importance of maintaining strict confidentiality of the emerging interim data; and the authorization of the DMC to exercise flexibility with respect to the statistical monitoring boundaries. Controversial issues include the proper role of the study sponsor, the extent of unblinding of data presented to the DMC, the relationship of the study statistician to the sponsor and investigators, the role of the DMC in evaluating proposed changes in an ongoing study, and the sharing of data among DMCs.

Session C
Interpreting Changes, Responder Analyses & Statistical Considerations for Patient-Reported Outcomes (PRO)
Joseph C. Cappelleri, PhD, MPH Pfizer Inc
Kathleen W. Wyrwich, PhD, United BioSource Corp.
Moderator: Naitee Ting

Patient-reported outcome (PRO) measures used for labeling and promotional claims must have the following:

- ❖ Evidence documenting their responsiveness
- ❖ Interpretation guidelines useful as clinical trial efficacy endpoints.

The recommended approach is to estimate the responder definition based on anchor-based methods, which will be discussed during the workshop. Confidence in a specific responder change threshold evolves over time and is confirmed by additional research evidence, including clinical trial experience; the responder change threshold may vary by population and context, and no one responder change threshold will be valid for all study applications involving a PRO instrument. This workshop will also cover how distribution-based methods can provide some insights on interpreting the amount of change that signifies an important change in PRO measures. Several ways to enhance the interpretation of PRO measures will be discussed and illustrated for the purpose of not only label claims but also, more generally, outside of label claims. These methods are based on cumulative distribution functions, area under the curve, reference groups, item-level content, Rasch models, ridit analysis, and mediation models. As interpretation is related to statistical analysis, three key statistical issues – multiple endpoints, composite endpoints, and missing data – common in PRO analysis will also be highlighted.

Monday Lunch (On Your Own) 11:30 AM - 1:00 PM

1:00 - 4:00 PM

Session B
Management of Regulatory Data Standards
David A. Evans, Octagon Research Solutions
Moderator: Kalyan Ghosh

Global pharmaceutical and biotechnology companies continue to struggle with the complexity of managing standards for the clinical information lifecycle, from trial design to regulatory submission. It is not only critical to define, collect, and maintain the data itself, but also the information about the clinical data: metadata. In the clinical information lifecycle, multiple types of metadata are relevant at any given point in time. Data metadata, Analysis metadata, standards metadata, systems metadata and study metadata are all types of metadata that require management and tracking throughout the lifecycle. To complicate the situation further, the metadata itself has a lifecycle. Mature organizations are now being challenged to manage the resulting chaos. Most organizations don't have a standard way to describe how data is collected, processed, analyzed and transformed over time. They have no mechanism for managing and communicating metadata standards across the enterprise.

This session will describe the sophisticated process and management functionality required to address the complex challenges of managing the lifecycle of data and metadata standards across the R&D organization. Major areas of the session will be focused on four main areas:

- ❖ Standards Management – creation and maintenance of standards metadata for data elements and supports flexible metadata describing collection, processing, transformation and lineage.
- ❖ Process Management – key standards governance activities including planning and execution, communication, issue management and reporting.
- ❖ Content Management – creation and management of supporting reference documents as well as storage and versioning of study and supporting documents.
- ❖ Standards Communication – machine-readable communication of standards metadata and study definition metadata between the repository and clinical systems across the clinical information lifecycle.

Session D 🕮
Group Sequential Design of Clinical Trials
Gordon Lan, PhD, Johnson & Johnson PRD
Moderator: Naitee Ting

This tutorial is a heuristic introduction to the design and interim analysis of clinical trials. A heuristic approach will be taken and mathematics will be kept to a minimum. Topics covered include:

- ❖ How much information is enough to start a clinical trial, or to stop one after an interim analysis? We will review two basic statistical methods for interim analysis - conditional power (CP) and group sequential methods. We will also discuss the idea of predictive power – a more sophisticated version of CP, for interim analysis and design of Phase III studies. A review of Group Sequential Methods will cover the classical Pocock boundary, O'Brien-Fleming boundary and the alpha spending functions. Numerical examples will be based on the output of a freeware created at the University of Wisconsin in Madison. http://www.medsch.wisc.edu/landemets/
- ❖ There are different ways to define the meaning of "a better treatment". Except for QoL studies, most researchers consider survival time as the hardest primary endpoint. The most popular methods for the comparisons of two survival distributions are the Kaplan-Meier curve and the log-rank test. When the proportional hazards assumption is violated, these two methods might deliver quite different messages and send misleading interpretations.

4 – 5 PM: Student Scholar Papers Moderator: Nandita Biswas

Exact meta-analysis approach for the common odds ratio of 2 by 2 tables with rare events by Dungang Liu, Regina Liu and Minge Xie

Adjustment for Measurement Error in Evaluating Diagnostic Markers by Using an Internal Reliability Sample by Matthew T. White and Sharon X. Xie

Using Split Samples and Evidence Factors in an Observational Study of Neonatal Outcomes by Kai Zhang, Dylan S. Small, Scott Lorch, Sindhu Srinivas, and Paul R. Rosenbaum

Tuesday December 6, 2011 8:30 – 11:30 AM

Session E 🕮
Analysis of Clinical Trial Data Using R
Prof. Din Chen, University of Rochester
Moderator: Walter R. Young

This tutorial provides a thorough presentation of biostatistical analyses of clinical trial data with detailed step-by-step illustrations on their implementation using R whose basis will be given. Examples of clinical trials based on the authors' actual experience in many areas of clinical drug development are presented. After understanding the application, various biostatistical methods appropriate for analyzing data from the trials are identified. Then analysis code is developed in a stepwise fashion using appropriate R packages and functions to analyze the data.

- Treatment comparisons with continuous/categorical endpoints: We start with simple two treatment comparisons using a t-test and extend this to multiple treatment comparisons (ANOVA) and then to ANCOVA with clinical covariates using "lm" function in R for continuous endpoints and "glm" for categorical endpoints.
- Longitudinal clinical trials: We illustrate longitudinal trials using R "lattice" graphical package and their analysis using linear mixed models for continuous endpoints (R function "lmer" from "lme4" package), generalized linear mixed model and generalized estimating equations (GEE) for categorical endpoints (R function "glmmPQL" from "MASS" package and "gee" from "gee" package).
- Meta-analysis in clinical trials: Fixed-effects and the random-effects models will be discussed for categorical and continuous endpoints using the powerful graphical feathers in R "meta" package.
- Bayesian analysis in clinical trials using MCMC simulations with Winbugs/R2Wingbugs/BRugs/rbugs and MCMCpack will be given.
- Additional topics: Analysis of bioequivalence, adverse events microarray data analysis in clinical trials.

Session G 🕮
Clinical Prediction Models
Prof. Ewout W. Steyerberg, Erasmus University
Moderator: Alfred H. Balch

Prediction models are increasingly developed in many medical fields, including cancer, cardiovascular disease, and many others. Methodological reviews have consistently shown many shortcomings in currently published models.

A number of requirements need to be fulfilled to develop a valid model. First, predictors need to be available that have a strong relationship with the outcome. Only then subjects with different outcomes can be discerned. Next, an adequate sample size needs to be available. Third, a sensible modeling strategy needs to be followed that systematically considers a number of steps, such as dealing with missing predictor values, transformation of continuous variables, selection of predictors and model specification, concern for overoptimistic estimation of effects, validation, and presentation of the final model. Ideally, a developed model is subsequently externally validated in another setting to assess its generalizability, and eventually tested for clinical impact. This final application may require simplification of a model to a simple decision rule.

Prediction model applications in the design and analysis of randomized clinical trials will be given, as illustrated for trials of patients with traumatic brain injury.

Tuesday Lunch (On Your Own) 11:30 AM - 1:00 PM

1:00 - 4:00 PM

Session F 🕮
Comparing Groups: Randomization and Bootstrap Methods Using R
Prof. Andrew Zieffler, University of Minnesota
Prof. Jeffrey Harring, University of Maryland
Moderator: Xiaoming Li

This tutorial introduces participants to the basics of randomization and bootstrap methods for making group comparisons. The instruction will focus on fundamental concepts as well as practical applications with an emphasis on the direct link between scientific research questions and data analysis with purposeful attention paid to the integration of design, statistical methodology and computation to propose answers to specific research questions regarding group differences. This mini-course is largely non-technical; however, some statistical theory underlying these methods will be addressed. In addition to presenting a conceptual overview, we will utilize examples to demonstrate the application of randomization and bootstrap methods within an experimental design and a quasi-experimental design framework focusing our attention on two-group and multiple-group comparisons in both between-subjects as well as a within-subjects design perspective. We also stress the construction of intervals and computation of appropriate effect sizes to augment the analysis. Instruction will consist of lecture, demonstrations of the software, and hands-on data analysis opportunities. Participants are expected to have only a basic knowledge of statistics and will gain hands-on experience with many aspects of randomization and bootstrap methods. Participants should bring a laptop equipped with R, available free from http://www.r-project.org.

Topics: – Exploratory Data Analysis using Kernel Density Plots
- – Randomization Tests
- – Bootstrap Tests
- – Bootstrap Intervals
- – Bootstrapping Effect Sizes
- – Within-Subjects Designs
- – ANOVA

Session H
Understanding Therapeutic Pathways Via Biomarkers and Other Uses of Biomarkers in Clinical Studies
Drs. Michael D. Hale & Scott D. Patterson, Amgen
Moderator: Alfred H. Balch

An overview of biomarker strategies applicable to clinical development, covering phases I-III, with an emphasis on early development studies will be given. This will include examples of successes and challenges associated with these approaches; study designs and analysis appropriate for different uses of biomarkers; practical considerations related to acquiring samples and developing or selecting a suitable assay; basic models useful for a quantitative approach to pharmacology, including the Hill and Gaddum models; regulatory considerations and recent FDA guidance's; and concepts around biomarker qualification. Intended audience includes people who desire to understand novel clinical approaches for early evidence of therapeutic pathway intervention in the drug development process, model-based approaches leading to dose selection based on desired degree of target impact, patient selection/enrichment using biomarkers, and matching clinical study design to intended use of biomarkers. Phase I dose finding studies have traditionally evaluated the relationship between drug exposure and toxicity at incremental doses until a maximum tolerated dose (MTD) has been determined. New therapeutic agents being developed today target a specific pathway, providing opportunities for strategies much richer than finding MTD, potentially including elements such as a priori selection of patients, verifying mechanism and measuring strength of pathway intervention, or for early indicators of desired pharmacodynamic activity in specific patients. For novel targeted therapies, understanding the relationship between drug exposure and the degree of target inhibition may provide proof of principle data for the intended mechanism of action of the drug and guide dose selection.

Targets are derived from research that includes correlation of pathway dysregulation with various disease processes. These pathways are usually present in tissues from normal healthy volunteers (NHV) as well as tissues from patients with the disease of interest. These pathways will be pharmacologically modulated, providing an opportunity to generate evidence of pathway interdiction early in the development process (phase I) with pharmacodynamic (PD) biomarkers, possibly in NHV. Development of these PD assays in appropriate tissues can positively impact understanding of a molecule's therapeutic potential in early development. When the degree of target inhibition can be measured by a PD marker, the PD response can be modeled as a function of the pharmacokinetics (PK). The model-based approach is useful for both confirming presumed biology, and identifying the drug concentration needed to yield a given PD response level. It is useful for dose selection by either taking a population approach, or customizing for a specific patient based on evaluation of a biomarker. Despite potential benefits of designing trials to include a prospective PK-PD assessment, evaluating a potential PD effect may be problematic. One needs accurate knowledge of the appropriate target and a robust assay to measure its effect.

Wednesday December 7, 2011 8:30 – 11:30 AM

Session I 🕮

An Introduction to Adaptive Designs With Applications to Clinical Trials

Michael Chernick, PhD, Lankenau Institute

Moderator: Xiaoming Li

Group sequential and adaptive designs for clinical trials go back to the latter half of the 20th century. However, it is in the first decade of the 21st century that Adaptive Designs have been made practical enough to be used in several phase II and phase III clinical trials. The importance of adaptive designs is evident from its place in the FDA's critical path initiative and by the conferences and books on the topic. Taylor and Francis Group just published a 27 chapter handbook on adaptive designs in pharmaceutical and clinical development. In the opinion of the author, one of the best and simplest applications is the two-stage adaptive sample size re-estimation trial. All too often fixed sample size designs have the sample size chosen based on tenuous assumptions with little or no supporting data. When this happens pilot studies are sometimes run to establish the necessary fixed sample size for the next study. But this can be wasteful. The same goal can be attained with an adaptive two-stage design with sample size re-estimation at the end of the first stage. This way all the data can be used for the final analysis and the trial could also be terminated at the end of the first stage for futility (this could be because of failure to meet efficacy or safety requirements or economic futility where the required sample size is so large that you cannot afford to complete it). The author will present an example of such a two-stage design that was used to show bioequivalence of two formulations of a testosterone supplement. The variety of adaptive designs that are currently being used in the pharmaceutical industry will also be covered.

Session K

Multiple Testing in Regulatory Applications

H.M. James Hung PhD & Sue-Jane Wang, PhD, FDA

Moderator: Ivan Chan

For regulatory applications, each clinical trial is conducted almost surely to entertain multiple objectives. As such, multiple comparisons are often performed in a clinical trial. As a clinical trial is regarded as a human experiment, an adequate control of experiment wise type I error is traditionally thought important to contain false positives. Statistical methodologies for ensuring a proper control are affluent in decades. As the clinical development program for a tested medical product is increasingly evolved, the statistical framework of inference pertaining to each clinical trial alone in relation to a family of multiple trials and to the issue of level of evidence becomes fuzzy. This tutorial will focus on visiting the statistical framework and paradigm of inference for multiple doses, multiple endpoints, subpopulations and multiple analyses within a single clinical trial or a family of clinical trials, which may be a multi-regional clinical trial or trials. Case examples will be presented to facilitate discussion. Topics to be covered are:

- Single versus multiple confirmatory placebo-controlled trials: Multiple end points, Multiple doses, Multiple analyses
- Active-controlled trial: Placebo is either present or absent, Non-inferiority and superiority analyses
- Adaptive design trial: Multiple dose regimens/multiple treatments, Subpopulations, Study objective, Key secondary endpoints

Wednesday Lunch (On Your Own) 11:30 AM - 1:00 PM

1:00 - 4:00 PM

Session J 🕮

Design and Analysis of Vaccine Studies

Prof. M Elizabeth Halloran, University of Washington

Moderator: Ivan Chan

Vaccine efficacy and effectiveness are usually measured by one minus some measure of relative risk in the vaccinated compared to the unvaccinated groups. The groups can be groups of individuals or groups of populations, depending on the vaccine effect of interest. Due to dependent happenings in infectious diseases, vaccination can produce several different kinds of effects at both the individual and the population level. In an individual, vaccination can induce a biologically protective response against infection and/or disease, and/or reduce the degree or duration of infectiousness for other individuals. Widespread vaccination in a population can produce indirect effects, even in individuals who were not vaccinated. Historically, interest focused on evaluating protective effects of vaccination. In this tutorial, we present a systematic framework for understanding the relation of the different vaccine effects to one another. We cover designs to estimate the different effects of vaccination. There include direct protective effects, indirect, total and overall effects, as well as the vaccine effect on preventing infection, disease, and reducing infectiousness. We discuss group-randomized designs to estimate indirect, total and overall effects of vaccination strategies. We touch on issues of evaluating immunological surrogates of protection. Some concepts are presented in a causal inference framework.

Session L 🕮

Graphical Approaches to Multiple Test Procedures

Frank Bretz & Willi Maurer, Novartis Pharma AG

Jeff Maca, Novartis Pharmaceuticals

Moderator: Wenjin Wang

Methods for addressing multiplicity are becoming increasingly more important and several multiple test procedures have been developed in the recent past that allow one to map the relative importance of different study objectives as well as their relation onto an appropriately tailored multiple test procedure, such as fixed-sequence, fallback, and gatekeeping procedures. We focus on graphical approaches that can be applied to common multiple test problems, such as comparing several treatments with a control, assessing the benefit of a new treatment for more than one endpoint, and combined non-inferiority and superiority testing. Using graphical approaches, one can construct and explore different test strategies and thus tailor the test procedure to the given objectives of an experiment.

We start with a general introduction to the problem of multiple comparisons that includes basic concepts and common methods for multiple comparisons. We then introduce iterative graphical approaches to construct new and extend existing multiple testing procedures. The resulting procedures are represented by directed, weighted graphs, where each node corresponds to an individual hypothesis, together with a simple algorithm to generate such graphs while sequentially testing the individual hypotheses. Such procedures can be based on either weighted Bonferroni tests, weighted parametric tests accounting for the correlation between the test statistics, or weighted Simes' tests. The approach is illustrated with the visualization of several common gatekeeping strategies. We also present several case studies to illustrate how the approach can be used in practice. In addition, we briefly consider power and sample size calculation to optimize a multiple test procedure for given study objectives. The methods will be illustrated using the graphical user interface from the gMCP package in R, which is freely available on the Comprehensive R Archive Network (CRAN).

TWO SIMULTANEOUS SHORT COURSES THURSDAY AND FRIDAY, DECEMBER 8-9, 2011

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

8:30–10:00 Lecture 10:00–10:20 Break 10:20–11:50 Lecture 11:50–1:10 Lunch 1:10–2:40 Lecture 2:40–3:00 Break 3:00–4:30 Lecture

Friday schedule will be a half hour earlier to facilitate students' transportation home

Modeling Survival Data: Extending the Cox Model 🕮

Terry M. Therneau, PhD, Mayo Clinic

Moderator: Alfred H. Balch

Text: *Modeling Survival Data: Extending The Cox Model*

In most medical work "survival analysis" is limited to the classic triad of the Kaplan-Meier curve, log-rank test, and Cox model. The available methods and software in the field has progressed far beyond that, and allows us to address clinical data much more completely.

This class will address extensions to the basic three. The first day will largely be focused on the text. These topics of time-dependent covariate and/or covariate effects, multiple events, and use of residuals have now become much better understood and should be part of every analyst's toolbox. The second day will focus on more recent additions of multi-state models (of which competing risks is a particularly interesting case), mixed effects survival models, and the use of marginal-structural models to deal with biased treatment assignments. All of the material to be presented is closely tied to actual research studies that have informed and educated the presenter. Examples will focus on the concepts, with more detailed R and/or SAS code provided in handouts.

1. Review: Survival data, model censoring, simple Cox models, stratification, tests, sample size
2. Extended Cox models
   - Time-dependent covariates
   - Alternate time scales
   - Multiple events
3. Marginal models for multiple and correlated events
   - Model choices
   - Dataset creation
   - Strengths and pitfalls
   - Extended examples
4. Model checking and validation Types of residuals Model issues:
   - Functional form
   - Proportional hazards
   - Influential points
   - Interaction between issues
5. Multi-state models
   - Competing risks and informative censoring
   - Relation of hazard and survival functions
   - Cumulative hazard (instantaneous risk) vs. cumulative incidence (lifetime risk)
6. Mixed effects Cox models
   - Assumptions, strengths, and weaknesses
   - Comparison/contrast to marginal models
   - Extended examples
7. Marginal-structural Cox models
   - Indication for treatment as a confounder and how these address it
   - Relationship to survey sampling methods Examples

Terry M. Therneau, PhD, is Professor and former Chair in the Division of Biostatistics and Bioinformatics at the Mayo Clinic. He has worked with medical researchers for over 35 years, with particular emphases in the areas of hepatology and liver transplant, hematology, and rheumatoid arthritis. The analysis issues therein have driven the need for enhanced analysis methods and software. He is the coauthor of over 200 medical papers and author of the survival package in R, along with contributions to the statistical literature.

Novel Approaches To Multiple Test Problems, With Applications To Adaptive Designs 🕮

Drs. Frank Bretz, Willi Maurer, & Jeff Maca, Novartis

Moderator: Wenjin Wang

Texts: *Multiple comparisons using* R

Multiple Testing Problems in Pharmaceutical Statistics

The issue of multiplicity often arises in the design and analysis of clinical trials. Common multiple test problems include comparing several treatments with a control, assessing the benefit of a new treatment for more than one endpoint, combined non-inferiority and superiority testing, or any combination thereof. One particular application arises in confirmatory adaptive design trials, when multiplicity adjustments are mandatory to account for adaptations made during the study. This two-day course will begin with the introduction of the basic fundamentals of multiplicity methodology, and continue through novel methods and strategies for addressing multiplicity concerns. These techniques will be demonstrated with several case studies and hands-on exercises.

Day1, Morning: Introduction and motivation for multiplicity adjustments

General concepts: Error rates, Single-step and stepwise test procedures, adjusted and unadjusted p-values, simultaneous confidence intervals, coherence and consonance. Basic construction methods: Union intersection and intersection union tests, closure principle, partitioning principle. Basic multiple comparison procedures: Bonferroni, Holm, Sidak, & Shaffer. Will also discuss Simes' based methodology: Simes, Hochberg, and Hommel.

Day 1, Afternoon: Graphical approaches to multiple comparison procedures

Introduction to graphical approaches to multiple comparison procedures for weighted Bonferroni-based closed test procedures, and strategies for multiple testing in clinical trials. This covers fixed sequence tests, fallback procedures and gatekeeping methods. Extension of graphical approaches to include weighted parametric and Simes tests. Case studies illustrate the use of graphical methods to construct and convey multiple testing strategies. Exercises to demonstrate the methodology.

Day 2, Morning: Multiple testing in general parametric models

Multiple testing in general linear models, with extensions to general parametric models relying on standard asymptotic normality results. Applications include simultaneous inference in standard regression and ANOVA models, generalized linear models, linear and non-linear mixed-effects models as well as survival data. Methods will be demonstrated with examples, and exercises.

Day 2, Afternoon: Multiplicity in adaptive designs

Introduction to confirmatory adaptive designs, and causes of multiplicity and bias in adaptive designs, repeated hypothesis testing in group sequential designs, multiple hypotheses testing in adaptive designs. Principles of adaptive testing procedures, including combination test principle and conditional error principle. Demonstration of multiple comparison techniques in real adaptive case studies, treatment selection designs.

Subpopulation designs: Methods will be demonstrated primarily using the R software package, although similar programming code in the SAS software packages will be given. Students are encouraged to bring laptops with the latest version of R installed, jointly with the gMCP and multcomp packages, from www.r-project.org. The course will assume familiarity with basic inferential methods.

Dr. **Frank Bretz** received his PhD from the University of Hannover, Germany, in 1999. After four years as Assistant Professor at the University of Hannover he joined Novartis 2004, where he is currently Global Head of the Statistical Methodology group. He has supported the methodological development in various areas of drug development, including dose finding, multiple comparisons, and adaptive designs. Since 2007 he is an Adjunct Professor at the Hannover Medical School.

Dr. **Willi Maurer** finished his studies of mathematics at the Swiss Federal Institute of Technology in Zürich with a thesis in decision theory in 1972. After postdoctoral studies, research and teaching activities at the Departments of Statistics at Yale University, Iowa State University and the University of Florida he joined the Medical Research Department of Sandoz as a clinical statistician in 1978 where he worked on projects in the CNS and immunology area before becoming head of Biostatistics Europe in 1983. In 2000 he was appointed head of the newly founded statistical methodology group in Novartis. He is especially interested in the development novel statistical methodology, related to multiplicity and adaptive designs that takes into consideration the interdisciplinary, ethical, economical and regulatory challenges to be faced in the design, analysis and interpretation of clinical trials. Since his retirement end of 2006 he serves as a statistical consultant to the Statistical Methodology group of Novartis' Development Dept.

Dr. **Jeff Maca** received his PhD in Statistics from Texas A&M University in 1997. He then joined Novartis Pharmaceutical Corporation. He spent 6 years as a trial and project statistician within the transplantation business unit designing Phase II and Phase III clinical trials. For the last 7 years, he has been part of the Statistical Methodology Group within the Biostatistics department providing statistical. His primary focus is in the area on design, conduct, and analysis of clinical trials using adaptive designs.

Please register online as early as possible. Do not mail this form unless absolutely necessary. Payment must accompany this form either by an included check or by a credit card number. Make checks payable to "ASQ NY/NJ Metropolitan Section" and mail to Manoj Patel; 114 Doric Court; Cary, NC 27519. The American Society for Quality (ASQ) is a tax-exempt organization. Federal Tax ID #39-09-12502. RECEIPTS and a CERTIFICATE OF ATTENDANCE will be distributed at the conference.

Surname	First Mr. ❑ Ms. ❑ Mrs. ❑ Dr. ❑ Prof. ❑	
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Phone	FAX	E-mail

Please Indicate Which Tutorial Sessions You Plan to Attend **A ❑ B ❑ C ❑ D ❑ E ❑ F ❑ G ❑ H ❑ I ❑ J ❑ K ❑ L ❑**

Conference Registration	Payment Must Be Made or Check Mailed On or Before October 1st	 November 1st	 Later or Onsite	Amount
Three Day Conference	$550	$670	$800	_____
One Day Registration, Monday, Tuesday, or Wednesday (circle 1)	$275	$325	$380	_____
Student (Proof of full time college status needed) or Retiree	$225	$275	$325	_____
One-Hour Registrant Reception with cold drinks and snacks Sunday 6:30 PM	**Free**		**Check box**	❑
Speaker Dinner, Monday 7:00 PM	45	$50	60	_____
Short Course Registration:				
❑ **Modeling Survival Data: Extending the Cox Model**	$740	$850	$970	_____
❑ **Novel Approaches To Multiple Test Problems (2 Texts)**	$795	$905	$1025	_____

Onsite short course registration requires advance e-mail or telephone notification so we can guarantee sufficient space and materials.

Havana Tower Rate: ($69 + 14% Tax + $10 Resort Fee) $88.66 Per Room Per Night

Arrival December: _____ Departure December: _____ King? ❑ or 2 Queen Beds? ❑

Rooms Must Be Reserved With this Form or on our Web Site on or Before November 30th to Get the Conference Rate

Tropicana Room Reservation (One Night Deposit of $88.66) Hotel Cancellation Policy: 2 Days Prior to Arrival _____

The 🕮 On The Tutorials And Short Course Titles Indicate That They Are Based On The Below Books

Book Author(s) and Title Onsite availability of books cannot be guaranteed unless you place an order in advance.	# Page	Year	ISBN 13 978-	Price ($) List	 Our	# of Copy	Total ($)
Taylor and Francis							
Bretz, Frank; Torsten, Hothorn; and Peter Westfall; Multiple Comparisons Using R	205	2010	1-584-88574-0	80	51		
Chen, Din; and Peace, Karl; Clinical Trial Data Analysis Using R	387	2010	1-439-84020-7	90	57		
Dmitrienko, Alex; Tramhane, Ajit; and Bretz, Frank; Multiple Testing Problems in Pharmaceutical Statistics	320	2009	1-584-88984-7	90	57		
Peace, Karl; and Chen, Din; Clinical Trial Methodology	420	2010	1-584-88917-5	90	58		
Springer							
Halloran, M. Elizabeth; Longini, Jr., Ira M.; and Struchiner, Claudio J.; Design and Analysis of Vaccine Studies	389	2010	0-387-40313-7	90	57		
Proschan, Michael; Lan, K. K. Gordon and Wittes, Janet; Statistical Monitoring of Clinical Trials A Unified Approach	272	2009	1-441-92134-5	85	54		
Steyerberg, Ewout W; Clinical Prediction Models	500	2009	0-387-77243-1	90	58		
Therneau, Terry M.; and Grambsch, Patricia M.; Modeling Survival Data: Extending the Cox Model	350	2000	1-441-93161-0	119	68		
John Wiley and Sons							
Chernick, Michael; and LaBudde, Robert; An Introduction to Bootstrap Methods With Applications to R	288	2011	0-470-46704-6	115	72		
Chernick, Michael; & Khutoryansky, Naum; Introduction to Adaptive Designs With Applications to Clinical Trials Using R	250	2012	0-470-40445-4	NA			
Ellenberg, Susan; Fleming, Thomas and DeMets, David; Data Monitoring Committees in Clinical Trials: A Practical Perspective	208	2002	0-471-48986-3	130	81		
Zieffler, Andrew; Harring, Jeffrey & Long, Jeffrey Comparing Groups: Randomization & Bootstrap Methods Using R	332	2011	0-470-62169-1	110	69		

Total Book Order (Books will be distributed during conference and short course registration) _____

Grand Total of Registration, Hotel Deposit, and Book Order _____

E-Mail Cancellations sent to registration@demingconference.com will be accepted until November 18th 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 cannot be cancelled. If a registrant cancels, his or her ordered books would be mailed.

Credit Card Type: ❑ American Express ❑ Master Card ❑ Visa ❑ Discover

Card Number: _____ Expiration Date: _____ Security Code: _____

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TRAVEL TO THE CONFERENCE

AIR: Check both Atlantic City (ACY) and Philadelphia (PHL) to search for the best fare and connections. The cheapest quick airport connection is the Tropiana shuttle, requiring reservations at 1-800-559-2040 or fax them at 1-215-616-5380. It meets all flights and charges $13 from ACY (cab is $27+) and $45 from PHL directly to the Tropicana. A tip is expected. 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 and Spirit, www.spiritair.com to ACY; and AirTran www.airtran.com (also to ACY), Frontier www.frontierairlines.com, Southwest, www.southwest.com, and USA 3000, www.usa3000airlines.com to PHL. 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, 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. The whole 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 R1 SEPTA connections from PHL to 30th Street. Friday through Sunday only direct service from NYC with a stop in Newark is available with the schedule on www.acestrain.com.

BUS: Call the Tropicana casino bus transportation department, (888) 275-1212 # 1 to find if there is service from your local neighborhood since 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 $3 jitney on Pacific Avenue to quickly get to the Tropicana. Greyhound has service directly to the Tropicana with a coin rebate, and a four-day open return from Philadelphia, NYC, Baltimore and Washington with details on www.luckystreakbus.com.

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. Don't park in the Tropicana's other garage, as it is tedious to get to the Havana Tower. We don't recommend valet parking, as this doesn't permit easy access to your car during your stay.

PROMOTIONS: Check your local Sunday paper for coupons. The Philadelphia Inquirer occasionally prints show and meal discount coupons both Friday and Sunday. Check www.tropicana.net to view their entertainment schedule and promotions as well as the websites of other casinos.

INFO: For maps, an events schedule, casino shows and general tourist info visit the Atlantic City Convention and Visitors Authority website at www.atlanticcitynj.com 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 clothes in NJ.

MEALS: Print a map of the Havana Tower on www.tropicana.net/conventions-Atlantic-City/images/TropMeetingSpace-HTower.pdf. Besides giving information on how to find registration, parking, and the meeting, it gives one an idea of the available restaurants and attractions. There are 22 restaurants at the Tropicana. The *Fiesta* Buffet offers reasonably priced, all-you-can-eat meals. There is *FIN,* a seafood restaurant, *Golden Dynasty*, a Chinese restaurant, and *Il Verdi* that offers gourmet Italian Cuisine. If one is in the mood for something more casual, *Hooters* is located conveniently on the first floor, adjacent to the Boardwalk. Outside of the Tropicana and along the Boardwalk are a variety of restaurants to suit any taste or budget, from classic seafood restaurants to *Burger King*. 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 at 2:30 PM. There is a subsidized Speaker Dinner on Monday and a free one-hour reception on Sunday with cold drinks, snacks, and a cash bar 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, 2012. The award will be announced and paid directly to the applicant on May 15, 2012. 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 winner and three members of his immediate family will be invited to an awards dinner in June 2012 in New Jersey but attendance is not mandatory and travel expenses to the dinner will not be paid. 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-two consecutive years.**