# PROGRAMME OF THE SIXTY-EIGHTH ANNUAL DEMING CONFERENCE ON APPLIED STATISTICS

**Sponsored by**
**AMERICAN SOCIETY FOR QUALITY**
**NY/NJ Metropolitan Section ~ ~ Statistics Division**
**AMERICAN STATISTICAL ASSOCIATION: Biopharmaceutical Section**
**December 3 – December 5, 2012: Three-Day Conference**
**Tropicana Casino and Resort, Havana Tower, Atlantic City, NJ**

**Short Courses: – December 6-7, 2012**

**1. Modeling Ordinal Data Profs. Alan Agresti University of Florida & Bernhard Klingenberg, Williams College**

**2. Missing Data in Clinical Trials Profs. Rod Little & Trivellore Raghunathan University of Michigan**

**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 2th and will be followed by a one-hour reception with cold drinks and snacks.**
**It will continue at 7:30 AM Monday December 3th through Wednesday December 5th and 8 AM Thursday December 6th.**
**ALL REGISTRANTS WILL RECEIVE A BOUND COPY OF THE AVAILABLE HANDOUTS FOR ALL SESSIONS.**
**Register and pay for both the conference and the Tropicana online at www.demingconference.com. This will give you an instant e-mail acknowledgement. Only if absolutely necessary, mail a check with your completed registration form on page 7 in this program. If checks are not postmarked on or before the early discounted registration date, you will be charged the next higher amount.**


Walter R. Young
Chairman
16 Harrow Circle
Wayne, Pa 19087

Meeting facilities are 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, safe, iron and board, complimentary wireless internet and gorgeous views of the Atlantic City skyline. Use the Havana Tower parking garage (sign says "The Quarter") on Brighton Avenue. Self or valet parking is $10 per stay for hotel guests.


- 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.

Mohamed Alosh is an Expert Mathematical Statistician and Biostatistics Team Leader at the Office of Biostatistics, Office of Transitional Sciences, Center of Drug Evaluation and Research at the FDA. His team supports the Division of Dermatology and Dental Drugs. Prior to joining the FDA in 1994, he held positions of Assistant and Associate Professor in Statistics at the College of Sciences, King Saud University, Riyadh, Saudi Arabia. His research interests include: integer-valued time series, modeling longitudinal data, handling missing data, addressing multiplicity issues and subgroup analysis in clinical trials.

Keaven Anderson has a PhD from Stanford University and is the head of Biostatistics late-stage oncology at Merck Research Laboratories where he has worked since 2003. He is the primary author and maintainer of the open source R package gsDesign for designing group sequential trials. He taught group sequential design for many years at the Joint Statistical Meetings, created on-line training at Merck, taught at the Deming Conference and in China, and presented at an on-line webinar for the ASA Biopharmaceutical Section. He previously worked in many drug, biologic and vaccine development areas at Merck and at Centocor/J&J and on cardiovascular epidemiology at the Framingham Heart Study.

Vance Berger holds degrees in statistics from Cornell University, Stanford University, and Rutgers University. His professional career has included work in the pharmaceutical industry (Janssen Research Foundation, Theradex, and some consulting for Pfizer), work in two centers of the Food and Drug Administration (Drugs or CDER and Biologics or CBER), and now he serves as a Mathematical Statistician for the National Cancer Institute. He taught in the past at Rutgers University, the Johns Hopkins University School of Public Health, and the University of Maryland. He is an active researcher, having written numerous scientific articles on the design and analysis of clinical trials in peer reviewed journals. He has also presented numerous lectures on this topic.

Björn Bornkamp studied Statistics in Dortmund, Germany (MSc and PhD), his research areas were Bayesian statistics and dose-finding studies. Since 2010 he is a Statistical Methodologist at the Integrated Information Sciences department at Novartis in Basel, working primarily on the design of dose-finding studies.

Frank Bretz has a PhD from the University of Hannover, Germany, in 1999. After four years as Assistant Professor there, 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.

Mark Chang is Vice President, Biometrics; AMAG. Previously, he held various positions in Millennium Pharmaceuticals. He is a co-founder of the International Society for Biopharmaceutical Statistics, was an executive member of the ASA Biopharmaceutical Section, and a member of the Expert Panel for the Networks of Centres of Excellence (NCE), Canada. He is a co-chair of the Biotechnology Industry Organization (BIO) Adaptive Design Working Group. He has many publications including five books. He has taught over ten statistical short courses. He is an adjunct professor of Boston University and 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 books with Professor Karl E. Peace.

Stephanie Green has a PhD from the University of Wisconsin. She has 30 years of experience in the design and analysis of cancer clinical trials. She is a Senior Director in Clinical Biostatistics for oncology development at Pfizer. She was the Deputy Director of the Southwest Oncology Group Statistical Center, and Affiliate Full Professor of Biostatistics at the University of Washington. Professional accomplishments include authorship on over 100 articles; President-Elect/President/Past President (1994-6) and Treasurer (2002-2004) of the Western North American Region of the International Biometric Society; member of the Editorial Board for the Journal of Clinical Oncology (2001-2003) and for Clinical Trials: Journal of the Society for Clinical Trials (2003-present); and an ASA Fellow since 1995.

Joseph Hogan is Professor of Biostatistics and on the Brown faculty since 1995. His research concerns the development and application of statistical methods for drawing causal inferences and handling incomplete data, with emphasis on applications to HIV and behavioral sciences. The current focus of his work is on HIV/AIDS in sub-Saharan Africa, specifically on analytic methods for large-scale observational data on individuals receiving HIV care in Kenya. The NIH funds his research. He was a member of the National Research Council Committee on Handling Missing Data in Clinical Trials. He is an ASA Fellow.

Mohammad. Huque is Division Director for the Division of Biometrics IV at the Office of Biostatistics under the Office of the Translational Sciences (OTS), Center for Drug Evaluation and Research (CDER), FDA since 1997. He directs the statistical review and research programs for therapeutic areas under the Office of Antimicrobial Products. He also supports the statistical review program of consumer behavior studies intended for non-prescription drugs. He is an ASA Fellow. He won the FDA Scientific Achievement Award in 1998 for his efforts in FDA decision-making in critical areas of multiple endpoints and multiple comparisons of clinical trials. He received his Statistics PhD from the University of Missouri in 1973. He is a member of the FDA committee that is currently drafting FDA guidance on multiple endpoints.

Jae K. Lee PhD is in Biostatistics at the University of Virginia. He has been working on a wide range of biostatistical research in molecular genetics and bioinformatics, including genetic population inference, DNA structure analysis, linkage association study, and high-throughput gene chip data analysis on various biomedical studies. In particular, he has pioneered the statistical development of small-sample microarray data analysis techniques such as LPE (local pooled error) and HEM (heterogeneous error model) for practical microarray applications, and COXEN genomic expression biomarker-based prediction of patients' chemotherapeutic responses in various cancers.

Cyrus Mehta obtained his PhD from MIT in 1973. He is President and co-founder of Cytel Corporation and Adjunct Professor of Biostatistics, Harvard University. He consults extensively with the biopharmaceutical industry on group sequential and adaptive design, offers workshops on these topics, and serves on data monitoring committees either as a voting member or as the independent statistician. He has led the development of the StatXact, LogXact and East software packages that are widely used in the biopharmaceutical industry and at academic research centers. He is a past co-winner of the George W. Snedecor Award from the ASA for the best paper in biometry. He is an ASA Fellow and was named the Mosteller Statistician of the Year by the ASA Massachusetts Chapter in 2000.

Kaitlyn Palys is a graduate student at Virginia Tech and an Associate Faculty Member Biometry Research Group NCI, who works with Vance Berger to evaluate the literature relevant to their research interests.

Herbert Pang is an assistant professor in the Department of Biostatistics and Bioinformatics at Duke University. He received his BA in Mathematics and Computer Science from University of Oxford in 2002 and PhD in Biostatistics from Yale University in 2008. His main research interests include classification and prediction methods, design and analysis of clinical trials, and biomarker discovery in clinical studies. He has published over 20 methodological and collaborative articles on statistics, genetics, genomics, bioinformatics, and clinical trials. He serves on the editorial board of the Journal of Clinical Oncology and the Journal of Biometrics and Biostatistics. He has also served as a reviewer on numerous leading journals in the field.

José Pinheiro has a PhD in Statistics from the University of Wisconsin at Madison. He worked at Bell Labs and Novartis Pharmaceuticals, before his current position as Senior Director in the Quantitative Decision Strategies group at Janssen Research & Development. He has been involved in methodological development in various areas of statistics and drug development, including dose-finding, adaptive designs, and mixed-effects models. He is a co-developer of the nlme library/package in S-PLUS and R for linear and non-linear mixed-effects models.

Richard Simon is Chief of the Biometric Research Branch of the NCI where he is chief statistician for the Division of Cancer Diagnosis & Treatment. He holds a PhD in Applied Mathematics and Computer Science from Washington University in St. Louis Missouri. He established the Molecular Statistics & Bioinformatics Section of the NCI, a multi-disciplinary group of scientists developing and applying methods for the application of genomics to cancer therapeutics. He is the architect of BRB-ArrayTools software for the analysis of microarray expression and copy number data; with over 13,000 registered users in 65 countries it has been cited in over 1500 publications. In recent years he has been involved in development of clinical trial designs for the development of new drugs and companion diagnostics.

Jianguo Sun (Tony) Sun received his Ph.D. in Statistics from the University of Waterloo in 1992 and is currently a professor at the University of Missouri. He has been working on failure time data analysis and longitudinal data analysis for over 20 years, especially on various statistical problems in AIDS studies. He has published many papers and in particular, wrote a book *Statistical Analysis of Interval-censored Failure Time Data* published by Springer in 2006. In addition, he has given many invited presentations of his work in both academics and industry.

Hongyu Zhao is the Head of the Biostatistics Division and the Ira V. Hiscock Professor of Biostatistics and Professor of Statistics and Genetics at Yale University. He has a B.S. in Probability and Statistics from Peking University in 1990 and PhD in Statistics from the University of California at Berkeley in 1995. His research interests are the applications of statistical methods in molecular biology, genetics, drug developments, and personalized medicine. He has published over 250 articles on statistics, human genetics, bioinformatics, and proteomics, and edited two books on human genetics analysis and statistical genomics. He is a fellow of the ASA, IMS, and AAAS, and won the Mortimer Spiegelman Award for a top statistician in health statistics under the age of 40 awarded by the American Public Health Association.

## Monday December 3, 2012 8:30 AM

### Keynote Address: Early History of the Deming Conference Professor J Stuart Hunter, Princeton University

Samuel S. Wilks hosted the annual Princeton Conference beginning in the early 1950's to increase interest in applications of statistics in and around the New Jersey area. Invited speakers were the statistical leaders of the day accompanied by active practitioners describing their work. This brief address discusses the personalities and topics that then ruled the day.

## 9 AM - Noon

### Session A

**Dose Finding Under Model Uncertainty: The MCPMod Approach**

**Drs. José Pinheiro Johnson & Johnson**

**Frank Bretz & Björn Bornkamp Novartis Pharma AG**

**Moderator: Naitee Ting**

Revolutionary advances in basic biomedical sciences over the past decade have mainly failed to translate into new approved drugs and treatments. The widespread perception is that clinical drug development needs to be substantially improved to allow the promises of the biomedical sciences revolution to be delivered as new therapies that will transform medical practice. One well-known issue in need of improvement in clinical drug development is poor dose selection for confirmatory trials resulting from inappropriate knowledge of dose response relationship (efficacy and safety) at the end of Phase 2.

We will discuss some of the key statistical issues leading to the problems currently observed in dose finding studies, including a review of basic methodologies traditionally used in these studies. A unified strategy for designing and analyzing dose finding studies under uncertainty about the underlying dose response model, denoted MCPMod, will be the major focus. The DoseFinding R package implementing the MCPMod approach will be presented and illustrated. Case studies based on real clinical trials, featuring functions in R package, will be used to illustrate the use of the methodology in practice.

### Session B 🕮

**Clinical Biomarker Model Development and Validation**

**Prof. Jae K. Lee Biostatistics, University of Virginia**

**Moderator: Xiaoming Li**

Development and validation of various biomarker models is critically demanded in current medicine for risk assessment, early diagnosis, prognosis prediction, and personalized therapeutic management of various human diseases. While a majority of recent biomarker developments are based on single gene targets, multi-gene biomarker models such as OncotypeDX and Mammaprint tests in breast cancer have proven their high and robust prediction performance in forecasting complex disease risks and outcomes of human patients. Consequently, discovery and validation of such multi-gene biomarker models has rapidly become one of the central issues in recent clinical sciences. The audience will learn different clinical and statistical requirements for biomarkers of different clinical utilities as well as statistical discovery, development, and validation strategies of such biomarker models. To achieve these learning objectives, we will briefly review novel statistical concepts and techniques in analyzing high-throughput molecular data, discuss several statistical methods in biomarker model discovery and development, and their validation strategies. In particular, we will pay a close attention to statistical issues in biomarker model validation with different clinical utilities such as prognostic and predictive biomarkers, especially since the latter biomarker models need to be demonstrated with a predictive value for a specific therapeutics as well as a prognostic value of patient's long-term outcome.

## Monday Lunch (On Your Own) Noon - 1:30 PM

## 1:30 - 4:30 PM

### Session C

**Applied Group Sequential Design For Clinical Trials**

**Keaven Anderson, Ph.D. Merck, North Wales, PA**

**Moderator: Alfred Balch**

Group sequential design is the most widely used and well-accepted form of adaptive design for confirmatory clinical trials. It controls Type I error for multiple analyses of a primary endpoint during the course of a clinical trial and allows early, well-controlled evaluation of stopping for strong efficacy results or futility. This course will review the basics of group sequential theory and demonstrate common applications of the method. The R package gsDesign and its graphical user interface will be demonstrated to provide the user with an easy-to-use, open source (no cost!) option for designing group sequential clinical trials. The user should leave the course with an ability to propose effective group sequential design solutions to confirmatory clinical trial design.

Topics covered include:

- Application of spending functions for selection of appropriate timing and levels of evidence for early stopping
- Confidence intervals
- Conditional power, predictive power and prediction intervals
- Time-to-event endpoints, including stratified populations and power for meta-analyses
- Binomial endpoints
- Longitudinal endpoints
- Superiority and non-inferiority designs
- Information-based sample size re-estimation
- Generation of publication-quality tables & figures describing designs

### Session D 🕮

**Interval-Censored Time-to-Event Data: Methods & Application**

**Profs. Din Chen & Tony Sun Universities of Rochester & Missouri**

**Moderator: Walter R. Young**

We provide a thorough presentation of statistical analyses of interval-censored failure time data with detailed illustrations using real data arising from clinical studies and biopharmaceutical applications. Specifically, we will start with some basic review of commonly used concepts and the problems of common interest to practitioners. Commonly used statistical procedures will then be discussed and illustrated as well as some recent development in the literature. In addition, some available software functions and packages in R and SAS for the problems considered will be discussed and illustrated. The specific topics to be discussed include:

- Biases inherent in the common practice of imputing interval-censored time-to-event data
- Nonparametric estimation of a survival function: Three basic and commonly used procedures will be discussed for nonparametric estimation of a survival function along with their comparison.
- Nonparametric treatment comparisons: We will start with generalized log-rank tests and then introduce several other recently developed nonparametric test procedures. A couple of R packages, available for the problem considered, will be discussed.
- Semiparametric regression analysis: For this part, we will first introduce several commonly used regression models including the proportional hazards model and the linear transformation model. The corresponding inference procedures are then introduced and illustrated using real data.
- Analysis of multivariate interval-censored failure time data: This part will discuss nonparametric estimation of joint survival functions and regression analysis of multivariate interval-censored failure time data. For the former, the focus will be on bivariate failure time data.

## Tuesday December 4, 2012 8:30 – 11:30 AM

### Session E

**Sensitivity Analysis For Missing Data In Randomized Trials**

**Professor Joe Hogan Brown University**

**Moderator: Naitee Ting**

Missing data continues to be a concern in modern clinical trials and observational studies. A 2010 NRC report (second Missing Data short course text) outlines a new framework for design, analysis and reporting of trials where some observations are missing. The fundamental problem in drawing inference from incomplete data is that assumptions about the distribution of missing responses cannot be checked empirically. We focus on the formulation and interpretation of sensitivity analyses, wherein sensitivity of estimates and inferences to assumptions about missing data can be represented. Key concepts related to handling missing data will be reviewed (such as missing at random, missing not at random), and common approaches to analysis will be critiqued (LOCF, random effects models, etc.). However the primary focus is on formulating and conducting sensitivity analyses for reporting treatment effects. We will present a detailed case study of a longitudinal clinical trial of treatments for schizophrenia. The study design calls for repeated measures over time, but dropout is appreciable and occurs for different reasons. We will provide background on the trial, compare and contrast potential methods of analysis, demonstrate a specific approach to sensitivity analysis, and provide guidance on interpreting and reporting results.

### Session F

**Selection Bias in Clinical Trials**

**Vance Berger PhD NCI & Kaitlin Palys Virginia Tech**

**Moderator: Kalyan Ghosh**

Randomized trials represent both the best medical research design and the greatest opportunity for misleading evidence to influence subsequent guidelines and prescribing decisions. This is due to the general uncritical acceptance of trial results. Careful scrutiny reveals that randomized trials can be subverted. We discuss one such opportunity for subversion, specifically selection bias that results from the ability of investigators to predict future allocations (a lack of allocation concealment) and recruit patients accordingly. That is, patients with better prognoses can be recruited when one treatment group is due to be allocated, and patients with worse prognoses can be recruited when the other treatment group is due to be allocated, thereby inducing confounding. The threats to allocation concealment that permit this prediction of future allocations are 1) the direct observation of treatment codes and 2) the prediction of future allocations based on knowledge of past allocations & restrictions on the randomization. Generally, only the first of these is considered, but we will instead focus on the second. We discuss novel methods to prevent, detect, and correct for this type of selection bias. We emphasize that the greatest obstacle to the widespread use of these methods is the spurious belief that randomized trials cannot be manipulated.

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

## 1:00 - 4:00 PM

### Session G

**Subgroup Analysis In Clinical Trials: Challenges & Opportunities**

**Drs. Mohamed Alosh & Mohammad Huque FDA**

**Moderator: Wenjin Wang**

Clinical trials are usually designed to assess the treatment effect in a general patient population expected to benefit from the treatment under investigation. However, the extent of benefit, if any, might vary by the subject's background characteristics including genotype, biomarker, clinical, and demographic factors, leading to differences in the benefits and risks across subgroups within the study population. Subgroup analyses in completed trials are usually carried out for checking consistency of study findings across subgroups and assessing whether there are differential treatment effects across subgroups that might impact how the treatment should be used. The main challenge in interpreting variability in the response across subgroups is the separation of true findings from those expected to arise due to chance-play alone. On the other hand, an anticipated heterogeneity in treatment effect across subgroups, based on findings from early clinical trials, or early stage in adaptive design, would provide an opportunity for designing a clinical trial with dual objectives of establishing efficacy claim for the total population or a targeted subgroup; thus increasing the chance of a successful trial. In this presentation we discuss: (i) the main issues encountered in the interpretation of subgroup analysis findings including quantification of chance-play findings and testing for subgroup-by-treatment interaction, and (ii) recent statistical strategies for the design and analysis of targeted subgroup trials where we consider the power interplay between subgroup and total population, subgroup enrichment design, recent approaches for addressing the multiplicity issues in such trials along with applications of these methodologies to clinical trials.

### Session H

**Statistical Analysis of Biomarkers**

**Professors Hongyu Zhao Yale and Herbert Pang Duke**

**Moderator: Kalyan Ghosh**

Recent advances in genomics and proteomics technologies allow researchers to observe gene and protein expression levels at the whole genome and proteome level. Such data present both great opportunities and challenges in identifying biomarkers useful for disease diagnosis and treatment. Major issues that arise from these data include the very large number of genes/proteins relative to the number of samples to be investigated, the strong dependency among these genes/proteins, the non-linear associations between the outcome, and the need to incorporate prior biological information and other relevant data sets. To address these challenges, statisticians have made considerable efforts in the past decade to develop methods for the design and analysis of genomics and proteomics data for biomarker identifications. We will describe classification, feature selection and prediction methods for the identification of biomarkers from high dimensional data. The methods covered will include but are not limited to naïve Bayes, regularized regression, support vector machines, random forests for a variety of clinical outcomes, such as binary, continuous and survival endpoints. This tutorial will provide a general review on the statistical methods and computational tools in this rapidly growing area. We will use several case studies to illustrate the key concepts and advances in this promising field.

**4 – 5 PM: Student Scholar and Attendee Poster Session Moderator: Nandita Biswas**

**A Split-and-Conquer Approach for Analysis of Extraordinarily Large Data. Xueying Chen, Rutgers University**

**Multiple Imputation Of Latent Counts From Heaped Self-Reported Observations of Daily Cigarette Consumption,** Sandra Griffith, University of Pennsylvania

**Applying Multiple Testing Procedures to Detect Changes in East African Vegetation, Nicolle Clements, Temple University**

**Introduction to Matching in Observational Studies Using Mixed Integer Programming, Jose Zubizarreta, Wharton School, University of Pennsylvania**

## Wednesday December 5, 2012 8:30 – 11:30 AM

### Session I 🕮
### Adaptive Clinical Trial Design and Simulation
### Mark Chang, PhD AMAG
### Moderator: Xiaoming Li

We will review the basic concepts and methods for adaptive clinical trial designs, including the group sequential, sample-size re-estimation, dose-escalation, and dose-finding trials. We will also discuss the adaptive design with missing data, adaptive design with a mixture of paired and unpaired data, adaptive design with both superiority and non-inferiority trials, adaptive design with multiple endpoints, and adaptive design based on sensitivity and specificity. Commonly used statistical methods for adaptive design will be introduced and compared, including various methods using combinations of stagewise p-values. Both frequentist and Bayesian adaptive designs will be included.

We will discuss implementations of adaptive trials, including interim monitoring using conditional power, dynamic randomization, and analyses of adaptive trials.

We will discuss basics of computer simulation techniques and how to apply them in clinical trials. Both simple illustrative examples and real life examples of classic and adaptive trials will be provided. The case studies will include cardiovascular, oncology, asthma, and image trials. We will use SAS and ExpDesign Studio to perform clinical trial simulation (CTS) in the classroom.

Controversies and challenges in adaptive trials will be extensively discussed. After the class, the attendees are expected to have basic knowledge to start adaptive trial designs with confidence.

### Session J 🕮
### Clinical Trials in Oncology
### Stephanie Green, PhD Pfizer Groton, CT
### Moderator: Ivan Chan

Study of new treatments is highly challenging, with history providing endless examples of incorrect conclusions based on faulty assumptions and inadequate methods of assessment. The introduction of randomized clinical trials was a turning point in the history of medicine, providing a sound method for determining the effectiveness of new therapies. Yet randomization cannot be used in all settings. There remains a role for single arm trials, such as for early studies with aim of gaining preliminary information about a new agent, or for studies in rare populations. In addition, randomization in itself is not sufficient for reliable results. In particular, the soundest design and most sophisticated analysis will not be sufficient if the data are not carefully and accurately collected or adherence to trial requirements is poor. It is also critical to understand potential pitfalls in the design of clinical studies. Issues such as choice of primary endpoint, trial size, stratification for important prognostic factors, use of historical information, model assumptions, blinding and choice of multiple testing approaches must be considered to assure a sound conclusion from the trial. After the primary analysis of a trial is completed, additional exploration is typically done to glean additional insight from the study. Pitfalls in analysis are also important to understand so as not to over-interpret observations. Issues such as those related to subset analysis, identification of prognostic groups, competing risks, outcome-by-outcome analysis, surrogate endpoints and meta-analysis may be critical to interpretation.

## Wednesday Lunch (On Your Own) 11:30 AM - 1:00 PM
## 1:00 - 4:00 PM

### Session K
### Adaptive Designs for Confirmatory Clinical Trials
### Cyrus Mehta, Ph.D. President, Cytel Inc.
### Moderator: Ivan Chan

The statistical methodology for designing adaptive group sequential clinical trials with sample size re-estimation, dose selection, and population enrichment will be given. Emphasis will be placed on strong control of type-1 error, a regulatory requirement for confirmatory trials. The major statistical tools for controlling type-1 error -- alpha spending, closed tests, weighted combination tests, and conditional error functions -- will be covered in detail. We will then show how some of these methods can be extended to obtain exact confidence intervals and unbiased point estimates in two-arm adaptive group sequential trials. The importance of simulation will be highlighted with the help of the new East-6 software running on the Architect platform. The methods will be illustrated by actual case studies that were activated after undergoing regulatory review. The tutorial will conclude with a discussion of the operational and logistical challenges of altering the future course of an on-going trial based on an unblinded interim analyses, and methods for preventing biased conclusions and building trust with regulatory agencies.

### Session L
### Cancer Clinical Trials in the Genomic Era
### Richard Simon National Cancer Institute
### Moderator: Alfred Balch

Developments in cancer biology and biotechnology provide unprecedented opportunities for the development of effective therapeutics and for utilizing them in a predictive manner. Taking advantage of these opportunities requires the development of new designs for clinical trials and re-evaluation of some existing paradigms for analysis strategies. The usual approach to the design and analysis of randomized clinical trials has been implicitly based on the assumption that qualitative treatment by covariate interactions is unlikely. Using the tools of genomic technology, it has now been firmly established that patients with the same stage and primary site of cancer harbor tumors that are widely divergent with regard to oncogenesis, pathogenesis and sensitivity to treatment. The assumption that large qualitative interactions are unlikely is no longer tenable for most areas of oncology therapeutics. The heterogeneity of tumors and availability of technology for characterizing the genomic basis of this heterogeneity is fundamental for therapeutics development and has important implications for the design and analysis of clinical trials. I will summarize new clinical trial designs that have been developed including

- targeted enrichment designs
- cross-validated adaptive signature designs
- prospective-retrospective designs using archived tumor specimens.

I will describe a predictive basis for clinical trials as a complement to inferential testing of a null hypothesis of no treatment effect. Both testing the null hypothesis and developing a predictive classifier of the patients most and least likely to benefit from the new treatment are important in many clinical trials.

## TWO SIMULTANEOUS SHORT COURSES THURSDAY AND FRIDAY, DECEMBER 6-7, 2012

**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**

## Missing Data in Clinical Trials 🕮

**Professors Roderick Little & Trivellore Raghunathan, University of Michigan**

**Moderator: Ivan Chan**

**Texts:** *Statistical Analysis with Missing Data*, 2nd Ed.

*The Prevention and Treatment of Missing Data in Clinical Trials*. National Research Council (2010). National Academy Press: Washington DC. A free pdf copy can be obtained from www7.nationalacademies.org/cnstat

We will discuss methods for the statistical analysis of data sets with missing values, emphasizing applications to clinical trials. Topics include: Definition and examples of missing data; assumptions about mechanisms, including missing at random; pros and cons of simple methods such as complete-case analysis and imputation; weighting methods; maximum likelihood and Bayesian inference with missing data; multiple imputation; computational techniques, included EM algorithm and extensions, and Gibbs sampler; software for handling missing data; missing data in common statistical applications, including regression, repeated-measures analysis. Selection and pattern-mixture models for nonrandom nonresponse. Sensitivity analysis for deviations from missing at random. Missing data in clinical trials: National Research Council report.

Prerequisites: Course requires knowledge of standard statistical models such as the multivariate normal, multiple linear regression, contingency tables, as well as matrix algebra, calculus, and basic maximum likelihood for common distributions, at the level of Statistical Inference, 2nd Ed by G Cassella & R L Berger.

Outline 1. Introduction. Patterns and mechanisms of missing data. Examples.

2. Naive Methods in Statistical Packages. Complete-case analysis, simple imputation, weighting. Properties and limitations.
3. Maximum likelihood and Bayes theory for complete and incomplete data.
4. Maximum Likelihood Computation: Factored Likelihood for monotone patterns, EM algorithm and extensions.
5. Multiple Imputation. Theory, Examples.
6. Stochastic Simulation Techniques for Monotone Patterns, Data Augmentation/Gibbs Methods.
7. Solutions for Some Important Missing Data Problems. Repeated measures models. Partially classified contingency tables. Regression with missing covariates. Pattern-mixture and selection models.
8. Missing data in clinical trials. Review of National Research Council report. Design and Conduct to Limit missing data. Analysis methods. Sensitivity analysis.

Learning objectives:

1. Understand definition of missing data and what constitutes a missing data problem.
2. Understand pros and cons of simple missing data methods.
3. Understand the definition of missing at random, and its implications for statistical analysis
4. Understand how maximum likelihood and Bayes apply in missing data problems.
5. Understand computational tools such as the EM algorithm and Gibbs' sampler as applied to missing data.
6. Knowledge of missing data software packages, and how they might be applied to common statistical models.
7. Understand techniques to limit missing data in the design and analysis of clinical trials, and principled methods for analysis.

**Rod Little** is Richard D. Remington Collegiate Professor in the Departments of Biostatistics and Statistics at the University of Michigan, and Research Professor at the Institute for Social Research. He has over 150-refereed publications, many on missing data, and is coauthor of the course text, which has become the standard statistical text on the subject. He recently chaired a National Academy panel on missing data in clinical trials.

**Trivellore Raghunathan** (Raghu) is Professor and Chair of the Department of Biostatistics, and Research Professor in the Institute for Social Research. He is a well-known expert on the analysis of missing data with missing values, having published many statistical articles on the subject, and developed the IVEware statistical package for multiple imputation.

## Modeling Ordinal Data 🕮

**Professor Alan Agresti, University of Florida**

**Professor Bernhard Klingenberg, Williams College**

**Moderator: Alfred H. Balch**

**Text:** *Analysis of Ordinal Categorical Data*, 2nd Ed.

This short course surveys methods for analyzing categorical response variables that have a natural ordering of the categories. Such data often occur in medical and public health disciplines (e.g., pain, quality of life, severity of a condition) and in the social sciences (e.g., for measuring attitudes and opinions). Topics to be covered include ordinal odds ratios and association measures for contingency tables, logistic regression models using cumulative logits, other ordinal logistic regression models (adjacent-categories logits, continuation-ratio logits, partial proportional odds, non-proportional odds, stereotype model), other multinomial response models (cumulative probit, log-log), marginal models and random effects models for clustered ordinal responses and count data, and Bayesian approaches to ordinal model fitting. Examples in the course notes show R, SAS, and Stata output. The presentation emphasizes interpretation of the methods rather than technical details, with examples including randomized clinical trials and social surveys such as the General Social Survey. Attendees are expected to have some familiarity with basic methods of categorical data analysis, including logistic regression models and chi-squared tests. Optional exercises will be given for a `practical session' the last session each day.

Topic 1: Logistic Regression Models Using Cumulative Logits

We show that biases can result from using ordinary regression with ordinal data, and then introduce ordinal measures that summarize effects for various ordinal models, such as local odds ratios, global odds ratios, and cumulative odds ratios. We then introduce the cumulative logit model having proportional odds structure, which has become the most commonly used ordinal model. Motivation is shown with a latent variable regression model. Special issues discussed include checking goodness of fit, power and sample size determination, the increased power that results from treating a variable as ordinal rather than nominal, and generalizing the model to permit non-proportional odds.

Topic 2: Other Ordinal Logistic Models

Ordinal models are introduced that use the logit link, focusing on adjacent-categories logit models, continuation-ratio logit models, and stereotype models. These models can also have proportional odds structure. Unlike cumulative logit models, these models still make structural sense when used with non-proportional odds and are easily adapted to Bayesian analyses and estimated with retrospective analyses. Connections will be shown between certain nonparametric tests using midranks (such as the Wilcoxon test and certain generalized Cochran--Mantel--Haenszel tests) and tests for parameters in the ordinal models.

Topic 3: Other Ordinal Multinomial Models

The cumulative link model generalizes the cumulative logit model to other link functions. The cumulative probit model is an important special case that is implied by an ordinary underlying latent regression model for a normal response. The cumulative log-log link provides a proportional hazards structure. Simpler interpretations result from fitting ordinary regression models for the mean response, but assuming multinomial rather than normal responses. However, ceiling or floor effects can cause bias.

Topic 4: Modeling Clustered Ordinal Responses

For clustered categorical responses, such as occur with repeated measurement of subjects in longitudinal studies, two types of models are popular: Marginal models that describe each response in the cluster in terms of explanatory variables, and random effects models that describe such effects at the cluster level. Marginal models are computationally awkward and are usually handled with generalized estimating equations (GEE) methodology. Random effects models can also be computationally difficult, but our focus here is mainly on simple random-intercept cumulative logit models. Other approaches are briefly mentioned, such as transitional models and conditional likelihood methods.

Alan Agresti is Distinguished Professor Emeritus, Department of Statistics; University of Florida. He is the author of six books and has conducted numerous short courses on categorical data analysis for universities, industry, and professional organizations in about 30 countries around the world. His awards include Statistician of the Year from the Chicago chapter of the American Statistical Association in 2003.

Bernhard Klingenberg is an associate professor of statistics at Williams College. His research includes the comparison of multivariate categorical data across samples with applications to adverse events and toxicity, simultaneous confidence intervals, and dose-estimation in clinical trials with a categorical response. He regularly consults with Novartis Pharmaceuticals.

**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.**

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| **Springer** | | | | | | | |
| Agresti, Alan & Meng, Xiao-Li; Strength in Numbers: Rising of Academic Statistics Departments in the U.S. | 365 | 2012 | 1-4614-3648-5 | 149 | 92 | | |
| Chang, Mark; Modern Issues and Methods in Biostatistics | 307 | 2011 | 1-441-99841-5 | 90 | 57 | | |
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| **John Wiley and Sons** | | | | | | | |
| Agresti, Alan; Analysis of Ordinal Categorical Data, Second Edition | 424 | 2010 | 0-470-08289-8 | 135 | 80 | | |
| Agresti, Alan; Categorical Data Analysis, Third Edition | 768 | 2012 | 0-470-46363-5 | 135 | 80 | | |
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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 to PHL is the Tropiano shuttle, requiring reservations at 1-800-559-2040. It charges $45 from PHL directly to the Tropicana. A tip is expected. There currently is a jitney from ACY to the Tropicana. 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 R1 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 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 $2.25 jitney on Pacific Avenue to quickly get to the Tropicana. If travel time is not of essence, explore Greyhound, which has open return service with a slot play bonus from 13 cities 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.

**POSTERS:** We will have poster session(s) to provide a forum for attendees to present concepts and issues of relevance to their peers. The abstract submission rules and presentation tips are on our website. Accepted abstracts will be posted on our website and in our transactions.

**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**: 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, 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, 2013. The award will be announced and paid directly to the applicant on May 15, 2013. 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 2013 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-three consecutive years.**