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

Sponsored by
AMERICAN SOCIETY FOR QUALITY
NY/NJ Metropolitan Section ~ ~ Statistics Division
AMERICAN STATISTICAL ASSOCIATION
Biopharmaceutical Section

December 7 – December 9, 2009: Three-Day Conference
Tropicana Casino and Resort, Havana Tower, Atlantic City, NJ

Short Courses: – December 10-11, 2009

1. Analysis of Clustered Categorical Data by Profs. Alan Agresti, University of Florida & B. Klingenberg, Williams College
2. The Statistical Evaluation of Surrogate Endpoints in Clinical Trials by Prof. Geert Molenberghs, I-BioStat, Universities of Hasselt & Leuven

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

REGISTRATION WILL BE ON THE FOURTH FLOOR OF THE HAVANA TOWER.
It will start at 6:00 pm on Sunday December 6th and will be followed by a one-hour reception with cold drinks and snacks.
ALL REGISTRANTS WILL RECEIVE A BOUND COPY OF THE AVAILABLE HANDOUTS FOR ALL SESSIONS.
See registration page and website: www.demingconference.com for further details.
You can register for the conference as well as reserve a room at the Tropicana at this site.

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Peter A. Young
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The conference will use the meeting facilities in the Tropicana's Havana Tower state-of-the-art complex with 500 hotel rooms where attendees will stay in soundproof rooms with climate control, direct-dial phones, cable color TV, coffee makers, hairdryers, refrigerators and gorgeous views of the Atlantic City skyline. Use the separate Havana Tower parking garage on Brighton Avenue for valet or indoor self-parking, $5 for unlimited entry and exit.

- 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.
- The casino is in a separate building connected by a bridge over Pacific Avenue.
- A free Diamond Club Card can offer rewards based on your play and may offer dining and show discounts.

Dhammika Amaratunga Ph.D. (Statistics, Princeton University) is is a Senior Research Fellow in Nonclinical Biostatistics at J&J PRD. Since the late 1990s, his primary focus has been on gene expression data analysis. He and his collaborators have written a book and have numerous publications in refereed journals; have taught several courses; and have given over 50 invited presentations over the last 10 years. He has been actively involved in a number of professional committees, including ASA's Committee on Award of Outstanding Application, PhRMA's Statistics Expert Teams on Pharmacogenomics and Biomarker Qualification and is the Director for PERI's webinar series on Statistics in Genomics.

Javier Cabrera Ph.D. is the director of Institute of Biostatistics and professor of the department of Statistics and Biostatistics at Rutgers University. He got his Ph.D. from Princeton University and has lectured in Statistics at Rutgers University, National University of Singapore and Hong Kong University of Science & Tech. He is author and coauthor of many publications in the areas of data mining and functional Genomics, including a book in Exploration and Analysis of DNA microarray and Protein array data. He is in the executive board of the Data Analysis working group for the DNA barcode of life. Research funded by NSF, NIH. Fulbright Fellow.

A. Lawrence Gould Ph.D. (Biometry, minor Medicine from Case Western Reserve University in 1967) worked at RTI until 1970, and at Merck Research Laboratories since then. Currently Senior Director, Scientific Staff. ASA Fellow since 1988. Areas of research interest include evaluation of safety data from clinical trials, application of data mining and Bayesian methods to pharmacovigilance, use of data mining to identify relationships that can be used to design future trials, meta-analysis, modeling and simulation techniques to reduce cost and unnecessary patient exposure in drug development, and application of decision science methods to drug development strategy.

Jaroslaw Harezlak Ph.D. (Biostatistics from Harvard University in 2005) worked for 2 years as a Research Fellow at the Harvard School of Public Health on high-dimensional problems in mass spectrometry proteomics research and then moved to the Division of Biostatistics at the Indiana University School of Medicine where he is currently an Assistant Professor. His main statistical research interests are in high-dimensional data, functional data and intensively collected data analysis as well as machine learning techniques. The majority of his collaborative effort is devoted to analyzing behavioral diary data collected in STD studies, and brain imaging data in neurocognitive studies of HIV patients.

Jay Herson Ph.D. (Biostatistics from Johns Hopkins in 1971). After working on cancer clinical trials at MD Anderson Hospital he formed Applied Logic Associates (ALA) in Houston in 1983. ALA grew to be a biostatistical-data management CRO with 50 employees when it was sold to Westat in 2001. Jay joined the Adjunct Faculty in Biostatistics at Johns Hopkins in 2004. His interests are interim analysis in clinical trials, data monitoring committees, and statistical / regulatory issues.

H. M. James Hung Ph.D. is Director of Division of Biometrics I, CDER, FDA. This provides services for 3 medical divisions of drug products (cardiovascular- renal, neurology, psychiatry). In his 20-year 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.

Jae K. Lee Ph.D. 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.

Xiaochun Li Ph.D. is an associate professor in the Division of Biostatistics, Indiana University School of Medicine and worked at Harvard School of Public Health and Dana-Farber Cancer Institute, as well as Eli Lilly. She has been working in the field of clinical trials and bioinformatics in cancer research for the past 10 years, including reporting of studies of all phases, design and analysis of high-throughput gene expression and protein arrays. Her tutorial text is a collective effort to showcase statistical innovations for meeting the challenges and opportunities uniquely presented by the analytical needs of high-dimensional data in cancer research, particularly in genomics and proteomics.

Robb J. Muirhead Ph.D. spent eight years on the faculty of the Department of Statistics at Yale University. He then spent 21 years in the Department of Statistics at the University of Michigan and was Chair for six years. In 1999 he moved to Pfizer's research headquarters in New London, CT where he is Senior Director in the Statistical Research and Consulting Center. He is known for his work in the area of multivariate statistical analysis and has published numerous papers and a 1982 Wiley book on the subject. He is a Fellow of the ASA, the Institute of Mathematical Statistics, and the Royal Statistical Society; and an elected member of the International Statistical Institute.

Tie-Hua Ng Ph.D. (Statistics from the University of Iowa in 1980) held several positions before joining the FDA in 1987. He left the FDA in 1990 to work for the Henry M. Jackson Foundation. In 1995, he returned to the FDA, Center for Biologics Evaluation and Research (CBER). He is currently a team leader supporting the Office of Blood Research and Review within CBER. His research interests include equivalence / noninferiority testing and Bayesian approach.

Nitin Patel Ph.D. in Operations Research from MIT where he has been a visiting professor for eleven years. He is a co-founder, with Cyrus Mehta, of Cytel Inc. where he is currently Chairman and Chief Technology Officer. He has published over 50 papers in professional journals and is a coauthor of a 2008 Wiley data-mining book. He talks on topics at the juncture of clinical trials and operations research including the rising role of simulations to accurately forecast the supply requirements of complex adaptive trials. He is a Fellow of the ASA & the Computer Society of India. He's served as vice president of the International Federation of Operations Research Societies & as president of the Operational Research Society of India.

Eve Pickering Ph.D. (Statistics, Rutgers University) is Associate Director in Research Statistics at Pfizer, Inc. in New London, CT. At Pfizer for 15 years, she was previously on the faculty at Wright State University in Dayton, OH. She has worked in all phases of clinical development, and contributed to projects in many therapeutic areas, including inflammation, ophthalmology, and neuroscience. Her current work focuses on biomarker fit-for-purpose validation and translation for clinical trials and pharmacogenomics.

Judith Quinlan began her career as a statistician in agriculture in Australia. She later moved to the UK and entered the pharmaceutical industry, initially a project statistician with GSK. Judith was with GSK for 10 years and went on to be Director statistics for Neurology and GI, and later to be Director of statistics for Biopharmaceuticals. The later position brought her to the US. Judith left GSK in 2008 and is now VP; Adaptive Clinical Trials at Cytel Inc.

André Rogatko Ph.D. (Genetics/Statistics from São Paulo University in 1983) is Director, Biostatistics and Bioinformatics at Samuel Oschin Comprehensive Cancer Institute, as of 10/2008. Previously, Dr. Rogatko had joint appointments at Emory University: Winship Cancer Institute; The Rollins School of Public Health and Department of Hematology and Oncology. He has also served as the Chairman and as Director of the Biostatistics Facility at the Department of Biostatistics at the Fox Chase Cancer Center. Dr. Rogatko has more than 100 published peer-reviewed articles, book chapters and computer applications in biostatistics and genetic epidemiology, and is a recognized expert in adaptive trials in oncology

Yi Tsong, Ph.D. is Deputy Director of Division of Biometrics VI, CDER, FDA, providing statistical services to center-wide drug safety assessment, pharmacological- toxilogic review, Integrated Review Team of QT Studies, Office of Generic Drug Products, Office of New Drug Quality Assessment, and Control Substance Staff. In his 25 years services at FDA, he worked in both clinical and non-clinical studies. He publishes research works on thorough QT studies in the two J. of Biopharmaceutical Statistics special issues on thorough QT studies (2008 and 2009). Of which he is the Co-guest Editor. He is an Associate Editor for Statistics in Medicine and J of Biopharmaceutical Statistics.

Sue-Jane Wang Ph.D. is Associate Director of Office of Biostatistics, Office of Translational Sciences, CDER, FDA. She has been with the FDA for 15+ years. Her office provides services for fifteen medical divisions of drug products in CDER on early phase and late phase adaptive designed clinical trials, and biomarker associated pharmacogenomics clinical trials. Her research interest has been focusing on adaptive designs including adaptive multi-regional trials, biomarker classifier, adaptive pharmacogenomics, and noninferiority methods. She is an elected member of ISI and an associate editor for Statistics in Medicine and for Statistical Biosciences Journal.

Shelemyahu Zacks Ph.D. is Professor of Mathematical Sciences at Binghamton University. He has published several books and over 170 journal articles in the areas of sequential analysis, detection of change-points, design and analysis of experiments, statistical control of stochastic processes, statistical decision theory, statistical methods in logistics and sampling from finite information. Dr. Zacks is a Fellow of the American Statistical Association, Institute of Mathematical Statistics, and the American Association for the Advancement of Sciences. He received a honorary Ph.D. from The University of Haifa in 2005.

Monday December 7, 2009
8:30 – 11:30 AM

Session A📖

High Dimensional Data Analysis in Cancer Research

Speakers: Professors Xiaochun Li & Jaroslaw Harezlak
Indiana University School of Medicine
Moderator: Walter R. Young

In an era with a plethora of high-throughput biological technologies, biomedical researchers are investigating more comprehensive aspects of cancer with ever-finer resolution. Not only does this result in large amount of data but also data with hundreds if not thousands of dimensions. Classically, the sample size **n** is much larger than the number of covariates **p**. The theoretical properties of the estimators in statistical models have mostly been discussed under the assumption of a fixed **p** and an infinite **n**. However, the advances in biological sciences and employed technologies has revolutionized the process of biomedical data collection and put us in the era of the number of covariates exceeding the number of observations, which poses challenges in the classical statistical paradigm. This tutorial will focus on variable selection and model building for prediction in high-dimensional setting. It will first give a brief overview of the various high-dimensional data sources, the challenges in analyzing such data, strategies in the design phase, and possible future directions. It will then focus on methodologies and issues surrounding variable selection and model building with special emphasis on penalization and shrinkage, including ridge regression, LASSO and its extensions, LARS and Dantzig selector as well as post-model selection inference. The tutorial will also present the tree-based ensembles, including classification and regression trees (CART), random forests and boosting for prediction and variable selection.

Session B

Dose Finding with Escalation with Overdose Control (EWOC) in Cancer Clinical Trials

Speaker: Professor André Rogatko, Cedars-Sinai Medical Center
Moderator: Alfred H. Balch

Traditionally, the major objective in phase I trials is to identify a working-dose for subsequent studies, whereas the major endpoint in phase II and III trials is treatment efficacy. The dose sought is typically referred to as the maximum tolerated dose (MTD). Several statistical methodologies have been proposed to select the MTD in cancer phase I trials. We focus on a Bayesian design, known as EWOC. The method is fully adaptive, makes use of all the information available at the time of each dose assignment, and directly addresses the ethical need to control the probability of overdosing. It is designed to approach the maximum tolerated dose as quickly as possible, subject to the constraint that the predicted proportion of patients who receive an overdose does not exceed a specified value. An important extension of EWOC is to allow the utilization of information concerning individual patient differences in susceptibility to treatment. This is the first method described to design cancer clinical trials that not only guides dose escalation but also permits personalization of the dose level for each specific patient. The extension of EWOC to covariate utilization was implemented in five FDA- approved phase I studies. Other aspects of EWOC to be discussed include choice of prior distributions and of cohort and sample sizes. The methodology will be exemplified with extensive simulation results and real life examples. We will go through all steps on how to design a trial with EWOC using free available software http://sisyphus.emory.edu/software.php .

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

1:00 - 4:00 PM

Session C

Design & Analysis Consideration of Thorough QT Studies

Speaker: Yi Tsong, Ph.D., CDER, FDA
Moderator: Ivan Chan

One of the most frequent adverse events for a drug to be removed from the market in recent years is death due to ventricular tachycardia resulting from drug-induced QT prolongation. The ICH Regulatory agencies requested all sponsors of new drugs to conduct a Thorough QT (TQT) clinical study, to assess any possible QT prolongation due to the study drug. The ICH E14 guidance released in May 2005 with the purpose to provide recommendations to sponsors concerning the design, conduct, analysis, and interpretation of clinical studies. However, it was short in providing details. For example, ICH E14 defined that drug-induced prolongation of QT interval as evidenced by an upper bound of the 95% confidence interval around the mean effect on QT of 10 ms. Furthermore, it defined that a negative thorough QT study is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QT interval excludes 10 ms. It leads to the requirement of showing non-inferiority of the test treatment to placebo at multiple time points. On the other hand, when the study result is negative, ICH E14 recommended to validate the negative result by showing that the study population is sensitive enough to show at least 5 ms prolongation of QT interval of a carefully selected positive control. The validation test is often carried out by demonstrating that the mean difference between positive control and placebo is greater than 5 ms at least one of the selected few time points. There is no detail provided in E14 on how to test and interpret. We will discuss the statistical interpretation of the design and analysis of E14 on thorough QT studies. We will also discuss alternative approaches proposed in the literature.

Session D📖

Extracting Reliable Information from Megavariate Data: Strategies and Case Studies

Speakers: Drs. Dhammika Amaratunga, J&J PRD
Javier Cabrera, Rutgers University
Moderator: Alfred H. Balch

Technological advances are rapidly increasing our capability to acquire data on a huge number of features simultaneously. How to properly analyze and interpret the megavariate ("small n, large p") data these advances generate remains a challenge but substantial progress is been made. In this presentation, we will outline a series of methods that are effective at extracting reliable information from megavariate data while overcoming the inherent danger of over fitting due to over-parameterization. Among the methods presented, special consideration will be given to a set of very recently developed resampling-based techniques that show promise. These include (1) an individual feature analysis to identify significant features using a method that borrows strength across features to increase efficiency, (2) a functional analysis procedure to identify significant pre-defined feature categories, (3) an ensemble classification procedure to identify similarities and/or dissimilarities among the samples and the features associated with any dissimilarities (both supervised and unsupervised classification will be discussed). In the biological sciences, some prominent examples of megavariate data are DNA microarray technology, DNA sequencing, mass spectroscopy and molecular imaging, technologies that are now gradually beginning to be more and more widely used in both nonclinical and clinical settings. We will present examples of strategies used in these areas. Software for the methods presented will be available, some through CRAN and Bioconductor, others through the authors' websites. Case studies will be used to guide the discussion.

Tuesday December 8, 2009
8:30 – 11:30 AM

Session E📖
Data and Safety Monitoring Committees In Clinical Trials
Speaker: Prof. Jay Herson, Johns Hopkins University
Moderator: Jackie Kennedy

This tutorial deals with best practices for data monitoring committees (DMCs) in the pharmaceutical industry rather than for the NIH-sponsored trials. The emphasis is on safety monitoring because this constitutes 90% of the workload for pharmaceutical industry DMCs. The speaker summarizes experience over 21 years of working as statistical member or supervisor of statistical support for DMCs. He provides insight into the behind-the-scenes workings of DMCs that those working in industry or FDA may find surprising. The introduction presents a stratification of the industry into Big Pharma, Middle Pharma and Infant Pharma that will be referred to often in this tutorial. Subsequent sections deal with DMC formation, DMC meetings and the process of serious adverse event (SAE) data flow. The tutorial's section on clinical issues explains the nature of MedDRA coding as well as issues in multinational trials. This will be followed by a statistical section that reviews and illustrates the various methods of statistical analysis of treatment-emergent adverse events including likelihood and Bayesian methods and dealing with multiplicity. The tutorial's review of biases and pitfalls describes reporting bias, analysis bias, granularity bias, competing risks, and recommendations to reduce bias. A description of DMC decisions goes through various actions and ad hoc analyses the DMC can make when faced with an SAE issue and their limitations. The tutorial concludes with emerging issues such as adaptive designs, causal inference, biomarkers, training DMC members, cost control, DMC audits, mergers and licensing and resignation from a DMC.

Session F📖
Bioinformatics in Biomedical Research
Speaker: Professor Jae K. Lee, University of Virginia
Moderator: Xiaoming Li

There has been a great explosion of biological data and information in recent years, largely due to the advances of various high-throughput biotechnologies such as shotgun sequencing, RNA gene expression microarray, protein mass spectrometry, and many other recent high-throughput biotechniques. Bioinformatics is the emerging science field concerned with the development of various analysis methods and tools for investigating such large biological data efficiently and rigorously. The success of many bioinformatics studies critically depends on the construction and use of effective and efficient heuristic algorithms, most of which are based on probabilistic modeling and statistical inference techniques. In this short course, we will discuss about the statistical challenges in these Bioinformatics studies and introduce several recently developed statistically concepts and techniques to overcome some of these challenges. The short course consists of two 1½ hour sessions with a short break between the two sessions:

Session I: Statistical Foundation & Applications In Large Biological Data Analysis

a. Statistical quality control of high throughput biological data
b. Statistical significance and tests for large biological data
c. High-dimensional biological data analysis: clustering & classification

Session II: Advanced Analysis For Large Biological Data

a. Statistical modeling for complex biological data
b. Experimental design for high-throughput biological studies
c. Statistical resampling methods for large biological data inference
d. Genetic network analysis on multi-gene systems

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

Session G
Safety Data Analysis
Speaker: Dr. A. Lawrence Gould, Merck Research
Moderator: Xiaoming Li

The analysis of safety data from clinical trials is as important as the analysis of efficacy data. The most appropriate analysis strategy for an adverse event depends on whether it was identified a priori, as not identified a priori but not 'rare', and as not identified a priori and 'rare'. Multiplicity affects the interpretation of analyses because many adverse events often will be reported. Hypothesis testing will be of limited help for adverse events not identified a priori because the many hypotheses are generated by the data. Quantifying the degree of risk will be more helpful, especially using Bayesian methods. This presentation describes some general considerations in planning for safety evaluation, presents some ways to summarize data using confidence or credible intervals, describes a Bayesian approach to interpreting the outcomes, and suggests a simple graphical way to address multiplicity. Once a drug has been approved for release to the marketplace surveillance continues, to identify rare potential toxicities that are unlikely to have been observed in the clinical trials carried out before approval. This surveillance accumulates large numbers of spontaneous reports of adverse events in spontaneous report databases. Recently developed empirical Bayes and Bayes methods provide a way to summarize the data in these databases, including a quantitative measure of the strength of the reporting association between the drugs and the events. Determining which of the particular drug-event associations, of which there may be many tens of thousands, are real reporting associations and which random noise presents a substantial problem of multiplicity because the resources available for medical and epidemiologic follow-up are limited. Bayesian screening techniques are useful in both the premarketing and post marketing contexts for identifying potential drug-event associations needing confirmation or refutation. The presentation will provide an overview of the methods with examples of their application.

Session H
Basic Concepts in Equivalence/Noninferiority Testing: Issues and Challenges
Speaker: Dr. Tie-Hua Ng, FDA
Moderator: Wenjin Wang

The objective of a noninferiority (NI) trial is to show that the test treatment or the experimental treatment is not inferior to the standard therapy or the active control by a small margin known as the NI margin. This tutorial will elaborate the rationale of choosing the NI margin as a small fraction of the therapeutic effect of the active control as compared to placebo in testing of the NI hypothesis of the mean difference with a continuous outcome. For testing the NI hypothesis of the mean ratio with a continuous outcome, a similar NI margin on a log scale may be used. This approach may also be applied in testing of the NI hypotheses for survival data based on hazard ratios as well as in the testing of the NI hypothesis with binary endpoints based on the odds ratio. An example in the thrombolytic area will be used for illustration purposes. Unlike the superiority trials (e.g., placebo-control trials), a poorly conducted NI trial (e.g., mixing up treatment assignment) would diminish the treatment difference that may exist and hence biases in favor of the test treatment. This is the fundamental issue in the NI trials. It is well recognized that multiplicity adjustment is not necessary in simultaneous testing for noninferiority and superiority. However, there will be more experimental treatments that are expected to have the same effect as the active control tested for superiority in simultaneous testing than would occur if only one null hypothesis is tested, thereby increasing erroneous claims of superiority. This leads to an increase in the false discovery rate for superiority.

Wednesday December 9, 2009
8:30 – 11:30 AM

Session I📖
Stage-Wise Adaptive Designs
Speaker: Prof. Shelemyahu Zacks, Binghamton University
Moderator: Jackie Kennedy

In many statistical problems the optimal design depends on unknown distributions. Adaptive designs utilize the available information to approximate the unknown optimal solution in stages or sequentially. We start with a few examples treated in the literature. An important problem in statistics is to estimate parameters with a prescribed precision; for example, to obtain fixed-width confidence intervals. Another variation of this problem is to test hypothesis with a prescribed power. Two-stage and sequential sampling procedures that attain these criteria are discussed. We show also in several cases how to determine the distributions of the stopping variables (random sample sizes) analytically. In contrast to simulations, analytic determination of these distributions allow us to determine **exactly** operating characteristics of the estimators or of test procedures. The tutorial will also discuss the problem of search of optimal dosages, when parameters of tolerance distributions are unknown. This is done in the context of adaptive designs for generalized linear models. Adaptive designs for sampling from finite populations are discussed too. Adaptive forecasting procedures are demonstrated for time-series analysis. In the areas of clinical trials, we discuss adaptive procedures in Phase I and Phase III. In Phase I most of the literature is focused on finding the maximum tolerated dose (MTD) of a new drug for chemotherapy. In Phase III the focus is on comparing the efficacy of a new treatment relative to a standard one. Problems of adaptive randomization procedures and of group sequential designs are discussed. In addition we cover also the topic of optimal allocation of resources (the Bandits Problem), change-points problems, and other sequential problems in industry, ecology and other related areas of applications.

Session J
Multivariate Statistics: Review Of Some Classical Theory, With Applications To The Pharmaceutical Industry
Speakers: Drs. Robb J. Muirhead and Eve Pickering, Pfizer
Moderator: Kalyan Ghosh

In addition to being the foundation for more recently developed, computer-intensive statistical methods for high-dimensional data, classical multivariate statistics continues to have useful and valid applications to many real data problems. This tutorial is a review of some classical results and procedures in multivariate statistical analysis – such as confidence regions for means, reference regions for multidimensional data, principal components analysis, canonical correlations, discriminant analysis and MANOVA. Some attention will be given to describing the robustness of the results and conclusions for the different approaches. An interesting application from the pharmaceutical industry involves the analysis of the liver function laboratory panel for drug safety testing, where changes in different sets of analytes within the panel may indicate different distinct safety concerns. We will also address applications in drug manufacturing (assessing tablet dissolution profiles to aid in developing the best formulation for a particular new compound), brain imaging biomarkers, pharmacogenomics (candidate gene studies and whole genome scan projects), and the FDA-mandated thorough QT studies. These examples will be used to illustrate concepts and procedures, with emphasis on graphical illustrations for clearer interpretation of results. Comparisons between packages and procedures available in SAS, R, and Matlab will be made, and example code will be provided. If time allows, we will also cover some Bayesian concepts applied to multiple co-primary endpoints and prediction problems, and methods of test construction.

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

Session K
Implementation of Adaptive Trials
Speakers: Dr. Nitin Patel & Judith Quinlan, Cytel Inc.
Moderator: Kalyan Ghosh

Industry has transitioned from discussions centered on theoretical aspects about the benefits, risks and challenges of adaptive designs, to today, when there are an increasing number of adaptive designs being used in practice. Growing industry experience with adaptive trials has also been accompanied by an increased understanding of what constitutes good adaptive practices. Not all adaptive trials are the same. However all adaptive trials require thoughtful planning for both design and importantly implementation. The recent PhRMA case study survey identified several barriers to adaptive trials that were related to implementation. These were data management, randomization and drug supply.

The focus of this presentation will be drug supply for adaptive trials. In particular we will emphasize the role of simulations in the evaluation of design options, and also their role in helping quantify the decision process for selecting the design best able to meet study objectives. However, as will be illustrated through an example, the decision to select the final design is not based solely on design performance measures, but is ultimately a balance between quantitative and qualitative measures that incorporate design performance and logistical considerations.

The role and benefits of simulation will be illustrated through a dose ranging example, where given a fixed sample size, the traditional approach was compared to two adaptive design options. In this example design options required working within the constraints of high drug costs, and limited drug quantity. The audience will see how simulations helped quantify the decision process and importantly, how the impact of drug supply, and randomization strategies was integrated into the decision process for the selection of the final design.

Session L
Issues and Challenges in Multiregional Clinical Trials
Speakers: Drs H. M. James Hung and Sue-Jane Wang
U.S. Food and Drug Administration
Moderator: Ivan Chan

In recent decades many clinical trials have been globalized in the sense that the patients participating in the trials are recruited from the clinical centers from many geographical regions. To market a medical product in a geographical region, reliance on the clinical data from other regions was long recognized but rigorous scientific and evidence-based evaluations of the efficacy and safety of the medical product were not formally considered until the scientific principles laid out in ICH-E5 were in place. Initially, the trial designs or clinical programs at large were based on the concept of bridging either on pharmacokinetic endpoint, pharmacodynamic endpoint or clinical endpoint. Due to limited patient sizes feasible for bridging study, after several years of experiences, it has been well recognized that simultaneously studying patients from multiple regions using the same protocol, the so-called global clinical trial strategy, yields better trial designs, better overall study power, better information borrowing and many intangible benefits. Global clinical trial can avoid the kind of difficulties inherent in bridging trial in interpretation of evidence that may not be based on randomized comparisons. However, global clinical trial designs possess another set of challenges, such as how to plan an adaptive global trial, how to interpret the apparent heterogeneity of treatment effects among the regions involved. This tutorial will give a brief overview of major advances in clinical programs involving multiple geographical regions. Topics to be covered include: bridging clinical trial designs, issues and challenges with planning a bridging trial, methods for analysis and interpretation of bridging trial, global trial designs, issues and challenges with planning global trial designs, analysis and interpretation.

TWO SIMULTANEOUS SHORT COURSES
THURSDAY AND FRIDAY, DECEMBER 10-11, 2009
GENERAL COURSE INFORMATION

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

SCHEDULE

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

Analysis of Clustered Categorical Data 🕮

Instructors: Professor Alan Agresti, University of Florida
Prof. Bernhard Klingenberg, Williams College
Moderator: Alfred H. Balch

Text: *Introduction to Categorical Data Analysis*, 2nd ed., Wiley, 2007

This course surveys methods for correlated categorical data, which occur with repeated measurement and other forms of clustering. After briefly reviewing logistic regression and standard methods for matched pairs, the main focus is on two types of models. The first type models the marginal distributions, with parameter estimation often handled with generalized estimating equation (GEE) methodology. The other type uses random effects to describe subject-specific conditional distributions. For each type, emphasis is on logit models for binary and ordinal responses. Examples, primarily biomedical in focus, use SAS (PROC GENMOD and NLMIXED). The presentation, which follows Chapters 10-13 of the "Categorical Data Analysis" (2nd ed., 2002) and Chapters 8-10 of the course text, emphasizes concepts rather than technical details. However, attendees should have some background in logistic regression.

1. Review of logistic regression

2. Models for Matched Pairs
Comparing dependent proportions: McNemar test et al.
Conditional vs. marginal models for binary matched pairs

3. Marginal Models
Marginal logit models for repeated binary response
ML, WLS, and GEE fitting methods
Cumulative logit modeling of repeated ordinal responses

4. Conditional Models: GLMs with Random Effects
Conditional logistic regression of clustered binary data
Generalized linear mixed models (GLMMs): ML fitting and inference
Logistic GLMMs for clustered binary and ordinal data

5. Additional Topics about Mixture Models

Alan Agresti is Distinguished Professor Emeritus, Department of Statistics; University of Florida. He is author of five books and has conducted numerous short courses on categorical data analysis for 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 assistant 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.

The Statistical Evaluation of Surrogate Endpoints in Clinical Trials 🕮

Instructor: Prof. Geert Molenberghs
I-BioStat, Universities of Hasselt & Leuven
Moderator: Ivan Chan

Text: *The Evaluation of Surrogate Endpoints,* Springer, 2005

Humanitarian and commercial considerations have spurred intensive search for methods to reduce the time and cost required to develop new therapies. Surrogate endpoints, i.e. measures that can replace/supplement other endpoints and that can be measured earlier, more conveniently or more frequently than the "true" endpoints are therefore essential. Regulatory agencies are introducing guidelines relating to this. But how can one establish the adequacy of a surrogate, in the sense that treatment effectiveness on the surrogate will accurately predict treatment effect on the true outcome? What evidence is needed, and what statistical methods most appropriately portray that evidence?
The validation of surrogate endpoints dates back to Prentice, who presented a definition and operational criteria. Freedman, Graubard, and Schatzkin supplemented these criteria with the proportion explained. Noting operational difficulties with the proportion explained, Buyse and Molenberghs proposed to use jointly the within-treatment partial association of true and surrogate responses, and the treatment effect on the surrogate relative to that on the true outcome. In a multi-center setting, these quantities can be generalized to individual-level and trial-level measures of surrogacy. Buyse and colleagues proposed a meta-analytic framework to study surrogacy at both the trial and individual-patient levels. This framework has been applied in a variety of settings. In the meantime, efforts have been made to converge to a common framework, based on information theory. This course presents an overview of these developments, with illustrations predominantly from the fields of ophthalmology, oncology, and mental health.

1. **Setting the Scene:** *The concept of surrogacy; Basic taxonomy; Key examples; Single-trial framework; The need for trial-level replication.*
2. **The Meta-analytic Framework:** *The framework for continuous outcomes; Issues in parameter estimation; Prediction.*
3. **Extensions and Specific Cases:** *Binary and survival endpoints; An ordinal surrogate for a survival true endpoint; A longitudinal surrogate for a survival true endpoint; Surrogacy in psychiatry; Longitudinal endpoints.*
4. **Towards Unification and Design Considerations:** *A suite of measures; Information theoretic unification; Design: Surrogate threshold effect; Substantive and methodological conclusions and outlook.*

Geert Molenberghs is Professor of Biostatistics at Universiteit Hasselt and Katholieke Universiteit Leuven in Belgium. He received the B.S. degree in mathematics (1988) and a Ph.D. in biostatistics (1993) from Universiteit Antwerpen. He published on surrogate markers in clinical trials, and on categorical, longitudinal, and incomplete data. He was Joint Editor of Applied Statistics (2001-4) and Co-Editor of Biometrics (2007-9). He was President of the International Biometric Society (2004-5), received the Guy Medal in Bronze from the Royal Statistical Society and the Myrto Lefkopoulou award from the Harvard School of Public Health. He is a founding director of the Center for Statistics. He is also the director of the Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-BioStat). Jointly with Geert Verbeke, he wrote several books on the use of linear mixed models for the analysis of longitudinal and incomplete data and taught numerous short and longer courses on the topic in universities as well as industry, in Europe, North America, Latin America, and Australia. They repeatedly received the ASA's Excellence in Continuing Education Award (2002, 2004, 2005, 2008). Besides the text, he wrote a book on missing data in clinical studies, with Michael G. Kenward, He is an elected Fellow of the ASA and an elected member of the International Statistical Institute.

HOTEL AND CONFERENCE REGISTRATION PLUS BOOK ORDERS

Please register 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. Only mail this form if absolutely necessary. If checks are not postmarked on or before the early discounted registration date, you will be charged the higher amount.

Please register as early as possible. Payment must accompany this form either by check, which must be included, or by credit card number. Make checks payable to "ASQ NY/NJ Metropolitan Section". 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. E-Mail, but no mail, confirmation will be sent.

Registration starts at 6 PM on Sunday December 6th, 7:30 AM December 7th through December 9th and 8 AM on December 10th. Checks and, **if absolutely necessary**, this form should be mailed to Peter A. Young; 16 Harrow Circle; Wayne, PA 19087-3852

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Conference Registration	Payment Must Be Made or Check Mailed On or Before October 1st	November 1st	Later or Onsite	Amount
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 & snacks Sunday 6:30 PM	**Free**		**Check box**	❑
Speaker Dinner, Monday 7:00 PM	45	$50	60	_____
Short Course Registration:				
❑ **Analysis of Clustered Categorical Data**	$740	$850	$970	_____
❑ **The Statistical Evaluation of Surrogate Endpoints in Clinical Trials**	$740	$850	$970	_____

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

Havana Tower Rate: $ 91.00 (Plus 14% Tax & $ 5 Occupancy Fee & $1 Phone = $109.74) Fee Per Room/Night

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Rooms Must Be Reserved With this Form or on our Web Site on or Before November 22nd to Get the Conference Rate

Tropicana Room Reservation (One Night Deposit of $109.74) Hotel Cancellation Policy: 2 Days Prior to Arrival _____

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Taylor and Francis							
Herson, Jay, *Data and Safety Monitoring Committees in Clinical Trials*	191	2009	1-420-07037-8	90	57		
Springer							
Burzykowski, Tomasz; Molenberghs, Geert; & Buyse, Marc, *The Evaluation of Surrogate Endpoints*	408	2005	0-387-20277-8	99	63		
Li, Xiaochun and Xu, Ronghui, *High-Dimensional Data Analysis in Cancer Research*	149	2009	0-387-69763-5	139	87		
John Wiley and Sons, Inc.							
Amaratunga, D & Carbrera, J, *Exploration and Analysis of DNA Microarray and Protein Array Data*	272	2003	0-471-27398-1	120	71		
Agresti, Alan, *An Introduction to Categorical Data Analysis*, 2nd Edition	400	2007	0-471-22618-5	115	69		
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Lee, Jae, *Statistical Bioinformatics for Biomedical and Life Science Researchers* **(Wiley Will Mail)**	420	**2010**	0-471-69272-0	90	56		
Molenberghs, Geert & Kenward, Michael, *Missing Data in Clinical Studies*	526	2007	0-470-84981-1	110	66		
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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. Adventure Trails, (609) 272-9140, gets one to the Tropicana from ACY for less than half the cost of a cab. There is also a slow, cheap NJ Transit service requiring a change in Pleasantville. The cheapest connection from PHL is the below referenced SEPTA, but this will take about two hours. Royal Airport Service, (888) 824-7767, is the recommended limousine from PHL, but renting a car may be cheaper (www.bnm.com). Also consider discount airlines not on the major search engines such as Spirit, www.spiritair.com to ACY and to PHL AirTran www.airtran.com (ACY also), Frontier www.frontierairlines.com, Southwest, www.southwest.com, & USA 3000, www.usa3000airlines.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, there is a #67 NJ Transit bus (requiring a change at Toms River) as well as train service (with two changes) to Atlantic City. 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 and SEPTA at 30th Street and PATCO at Lindenwald. Free shuttle busses meet all trains and provide direct service to the Tropicana. www.njtransit.com/pdf/rail/current/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 $1.50 jitney on Pacific Avenue to quickly get to the Tropicana. Greyhound's service directly to the Tropicana with a coin rebate, and a four-day open return from Philadelphia, NYC, Baltimore and Washington is given on www.greyhound.com/home/en/DealsAndDiscounts/LuckyStreakNJ.aspx.

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 Havana Tower garage (both self-park and valet) is on your left after 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 Bureau 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 Atlantic and Michigan or strolling on the Boardwalk to the pier shops at Caesars. Remember there is no sales tax on clothes in NJ.

MEALS: We suggest printing a map of the Havana Tower on www.tropicana.net/images/map.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 eight restaurants besides those in the Havana Tower. The *Fiesta* Buffet offers reasonably priced, all-you-can-eat meals. *The Seaside Café* offers a wide variety of options 24 hours a day. *Wellington* and *Dynasty* offer their respective takes on food from the Far East, while *Il Verdi* 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 will provide a continental breakfast before our morning sessions as well as afternoon refreshment breaks at 2:30 PM. Also, there will be an optional subsidized Speaker Dinner on Monday and a 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 and complete rules are on the conference website and background information is on www.metro-asq.org. The application must be submitted after the conference and before April 1, 2010. The award will be announced and paid directly to the applicant on May 15, 2010. 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 2010 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 consecutive years.**