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

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

December 6 – December 8, 2010: Three-Day Conference
Tropicana Casino and Resort, Havana Tower, Atlantic City, NJ

Short Courses: – December 9-10, 2010

1. Bayesian Adaptive Methods for Clinical Trials by Prof. Brad Carlin, University of Minnesota and Scott Berry, Berry Consultants
2. SAS for Mixed Models by Profs. Ramon Littell, University of Florida and Walter Stroup, University of Nebraska

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 5th 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.

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

Non Profit Organization
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Permit Number 9

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 indoor self-parking, $5 for unlimited entry and exit. Valet is $5 extra.

- 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.

David Banks Ph.D. (from Virginia Tech in 1984) is a professor in the Department of Statistical Science at Duke University. He has taught at the University of Cambridge and Carnegie Mellon University; he also spent six years in the federal government. His research interests include metabolomics, network models, data mining, and statistical metrology. He is past-editor of the Application and Case Studies section of the Journal of the American Statistical Association, and serves on the Board of the Directors of the ASA.

Mark Chang Ph.D. is the executive director, Biostatistics and Data Management, AMAG Pharmaceuticals, with over 15 years of experience as a statistician in the field of clinical trials. In addition, he has over 4 years of teaching experience as assistant professor. He is a co-founder of the International Society for Biopharmaceutical Statistics, an executive member of ASA Biopharmaceutical Section, and a member of Expert Panel for the Networks of Centres of Excellence, Canada. He is a co-chair of Biotechnology Industry Organization Adaptive Design Working Group. His publications include four books. He serves on Editorial Boards for three Journals. Dr. Chang is an elected Fellow of American Statistical Association.

Alex Dmitrienko, Ph.D., Research Advisor, Eli Lilly and Company, has been actively involved in biostatistical research and has published over 60 papers on multiple testing procedures, group sequential inferences and analysis of safety data in clinical trials. Besides the text for the tutorial, he has authored/edited two SAS Press books (Analysis of Clinical Trials Using SAS, Pharmaceutical Statistics Using SAS. He has taught over 20 short courses, including an award-winning full-day course on analysis of clinical trials at Joint Statistical Meetings. He is an Associate Editor for Statistics in Medicine and a Fellow of the ASA.

Scott Evans Ph.D. is a Principal Investigator and Senior Research Scientist at Harvard University. He has received the "Distinguished Collaborative Statistician Award" for significant statistical contributions to HIV research and a Recognition Award for contributions of statistical expertise from the Harvard School of Public Health. Dr. Evans teaches "Clinical Trials" at Harvard and has taught short courses at the JSM, BASS, SCT, the FDA-Industry Workshop and in countries such as Japan, Brazil, and Australia. Dr. Evans serves on an FDA Advisory Committee and serves and chairs numerous Scientific Advisory Committees and Data Monitoring Committees.

Diane Fairclough Dr. PH. is Professor in the Department of Biometrics and Informatics, Colorado School of Public Heath and director of the Biostatistics Core of the Colorado Health Outcomes Program at the University of Colorado Denver. She is currently President of the International Society of Quality of Life Research (ISOQOL). Her research interests include the design and analysis of longitudinal studies with missing data with a focus on patient reported outcomes. She has over 170 peer-reviewed publications,

Jason Hsu Ph.D. is a professor in the Department of Statistics at the Ohio State University. He works in the area of multiple testing and multiple comparisons. Since 1998, the approach he has emphasized is to connect methodological development with emerging biomedical issues. Besides fundamental concepts and techniques, his current interests include analysis of multiple endpoints data, and pharmacogenomics.

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

Karl E. Peace, Ph.D. is Senior Research Scientist, Professor of Biostatistics and the Georgia Cancer Coalition Distinguished Cancer Scholar in the Jiann-Ping Hsu College of Public Health at Georgia Southern University. His distinctions include ASA Fellow, the APHA Statistics Section Award for contributions to industry and both the Georgia and US Congresses have cited him for contributions to drug R&D, public health and philanthropy. He is past Chair of the PMA Biostatistics Subsection, the ASA's Biopharmaceutical Section and BASS' founder. He is Chair-Elect of the Statistics Section of the APHA, and chairs several DSMBs. He recently published his autobiography: Paid In Full (www.plowboy-press.com).

Wan Tang Ph.D. is Assistant Professor of Biostatistics at the University of Rochester. He has been working closely with investigators from the Department of Psychiatry and School of Nursing at the University of Rochester on a range of projects and grant submissions. His research interests focuses on semiparametric modeling of categorical and count responses for longitudinal studies, smoothing methods, and analysis of data with missing values.

Yi Tsong, Ph.D. is Deputy Director of Division of Biometrics VI, CDER, FDA, The Division provides statistical services to center-wide pharmacology-toxicology studies, QT studies, generic drug products trials, new drug and post-marketing quality assessment, and control substance studies. In his 21 years at FDA, he worked in both clinical and non-clinical studies. He has published research works in Statistics in Medicine, J. of Biopharmacological Statistics and Biometrical J. He guest edited J. of Biopharmaceutical Statistics special issues on thorough QT studies, non-inferiority trials, non-clinical statistics and stability studies. He serves as an Associate Editor for Statistics in Medicine and J of Biopharmaceutical Statistics.

Venkat Venkatasubramanian Ph.D. is a Professor of Chemical Engineering at Purdue University. His research and educational contributions have been in process modeling and control, risk analysis, molecular products design and pharmaceutical informatics. Venkat has published over 180 peer-reviewed papers and given 130+ invited lectures including 20 keynote/plenary presentations. His contributions have been recognized by a number of awards, the most recent one being the Computing in Chemical Engineering award in 2009 from the American Institute of Chemical Engineers. Venkat is an Associate Editor of Computers and Chemical Engineering.

Brian L. Wiens, Ph.D., is Director of Confirmatory Biostatistics at Alcon Laboratories in Fort Worth, Texas. He has been actively involved in biostatistical research and has published dozens of papers on multiple testing procedures, non-inferiority and other topics in design and analysis of data in clinical trials. He has also co-authored numerous articles in the medical literature detailing results of clinical trials. He is an Associate Editor for *Statistics in Biopharmaceutical Research* and former chair of the Biopharmaceutical Section of the ASA.

Monday December 6, 2010 8:30 – 11:30 AM

Session A 🕮
Principles and Techniques of Multiple Testing and Multiple Comparisons
Speaker: Jason C. Hsu, The Ohio State University
Moderator: Naitee Ting

This tutorial is about fundamental concepts and techniques of multiple testing, in clinical trials and bioinformatics. It will discuss Familywise Error Rate (FWER), generalized Familywise Error Rate (gFWER), and various versions of False Discovery Rate (FDR, Fdr). Error rate control issues are:

- *True*, *average*, or *worst case* scenario (to sup or not to sup)
- *Number* or *proportion* of incorrect rejections
- *Conditional* or *unconditional*
- *Tail probability* or *expectation*

It will describe the multiple test construction techniques of

- Closed Testing
- Partition Testing

Familiar methods such as Holm's and Hochberg's stepwise tests turn out to be special cases of partition testing. Using the analysis of Multiple Endpoints data, it will be shown that Partition Testing has some advantage over Closed Testing (Gatekeeping) in terms of simplicity and power (Liu and Hsu 2009 *JASA*). The rush to meet the challenge of Bioinformatics seems to have occasionally overlooked fundamental principles of multiple testing. Using testing for association between biomarkers and drug response or adverse events as an example, it will be shown that common permutation tests don't control multiple testing error rates (without assumptions on the joint distributions of gene expression levels or SNP alleles between phenotypes).

This is not a cookbook tutorial, by illustrating the application of fundamental principle and techniques in

- Multiple primary-secondary endpoints efficacy testing
- Genome-Wide Association Studies (GWAS)

The objective is to guide the participant to decide on an error rate to logically control, and to confidently control it.

Session B
Sample Continuous Manufacturing and Large Sample Dose Content Uniformity Acceptance Plan
Speakers: Yi Tsong, FDA & Venkat Venkatasubramanian, Purdue University
Moderator: Alfred H. Balch

The current state of largely batch oriented manufacturing has led to higher end product variability, scale up difficulties, poor utilization of capital investment, losses due to batch rejections and related problems. In part this is because quality assessments and specifications of finished product are carried out after the batch is produced which can lead to whole batch rejection. Currently, modifications are often needed after scale up. While there are significant benefits to continuous manufacturing, the transition to this new paradigm is not an easy one.

We will begin with an overview of the technologies, challenges and solution methodologies for the various unit operations in the continuous manufacture of solid oral dosage forms and quality assessment of the finished products.

There are improvement opportunities at several levels, ranging from the development of in-line sensors to modeling and real-time control and integration of unit operations, in-line quality assessment. Statistical methodologies related to these opportunities will be discussed. Topics to be discussed include batch vs. continuous manufacture, real-time sensing and monitoring, modeling and informatics issues, design-space optimization, feedback and feed-forward control, exceptional events management, hardware and software integration, small sample quality assessment and medium to large sample in-line quality assessment of finished products. As well as parametric and non-parametric approaches for quality assessment. .

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

1:00 - 4:00 PM

Session C 🕮
Gatekeeping Procedures in Clinical Trials
Speaker: Alex Dmitrienko, Eli Lilly
Moderator: Kalyan Ghosh

The tutorial gives a review of multiplicity issues arising in clinical trials with hierarchically ordered objectives, including analysis of trials with primary and secondary endpoints, multiple dose-control comparisons and multiple subgroups. It introduces a class of multiple testing procedures for complex hypothesis testing problems of this kind, known as gatekeeping procedures. Gatekeeping procedures have been widely used in clinical trials with multiple objectives due to the fact that they control the overall Type I error rate and enable trial sponsors to enrich product labels by including information on relevant secondary objectives. Topics include:

1. Gatekeeping procedures with simple logical relationships among families of hypotheses (serial and parallel gatekeeping procedures), including a general method for constructing multistage parallel gatekeeping procedures based on a variety of powerful tests such as p-value-based tests (e.g., Hochberg test) and parametric tests (e.g., Dunnett test). Examples include gatekeeping procedures for trials with multiple primary/secondary endpoints, and general population and multiple subpopulation analyses.
2. Gatekeeping procedures with general logical relationships among families of hypotheses, including a mixture-based method for defining gatekeeping procedures for "multi-dimensional" hypothesis testing problems based on powerful p-value-based and parametric tests, e.g., gatekeeping procedures for trials with multiple dose-control comparisons and multiple primary/secondary endpoints, and multiple dose-control comparisons with non-inferiority/superiority analyses.

It has a well-balanced mix of theory and applications with case studies based on real clinical trials. It covers regulatory considerations, including the FDA guidance on multiple endpoints as well as software implementation of gatekeeping procedures using SAS and R software.

Session D 🕮
Applied Categorical and Count Data Analysis
Speakers: Profs. Wan Tang & Xin Tu, University of Rochester
Moderator: Xiaoming Li

This tutorial will discuss data analysis of ordinal, categorical, and count data, with an array of illustrative examples including programming codes. It will cover (1) commonly used methods for contingency tables; (2) logistic regression models for categorical responses, including exact logistic models and Firth's bias reduced methods; and (3) probit, complementary log-log models and models for general polytomous ordinal and categorical.

Poisson regression will be discussed for count responses. How to detect and correct overdispersion using scaled and sandwich variance estimates will be discussed as will negative binomial, and zero inflated Poisson, and zero-inflated negative binomial as alternatives for more complex mixture distributions. Poisson regression will be applied to general multi-way contingency tables.

For longitudinal studies with repeatedly measures outcomes from the same subject over time, focus will be on the two most popular mixed effect models and generalized estimating equations. For validity and reliability data, how to assess the accuracy of an ordinal test when the true status of a binary outcome is known, using the theory of receiver operating characteristics (ROC) curves will be discussed. If the true status is not available, concepts of Cronbach's coefficient alpha and Inter-rater reliability from reliability theory are introduced. The tutorial concludes with a discussion on addressing missing values.

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

Ms. Chia-Hao Wang, University of Pennsylvania, School of Medicine "Mediation Analysis Using G-estimation Approach Under Log-linear Structural Nested Mean Models"

Mr. Michael Baiocchi, University of Pennsylvania, Wharton School, "Near/Far Matching: Quantifying the Benefit of High Level Neonatal Intensive Care Units"

Mr. Tuan Nguyen, Rutgers University. "Modeling And Nonparametric Methodology For Count Data In Drug Studies"

Tuesday December 7, 2010 8:30 – 11:30 AM

Session E 🕮

DESIGN AND ANALYSIS OF STUDIES OF HEALTH-RELATED QUALITY OF LIFE

Speaker: Professor Diane L. Fairclough, UCHSC

Moderator: Walter R. Young

Assessment of health-related quality of life (HRQOL) is being incorporated into clinical trials with increasing frequency. This workshop is intended to answer the following questions: What are the similarities and differences between HRQOL and other traditional clinical trial endpoints? What are the specific issues in the design, conduct, analysis and reporting of studies with HRQOL assessment? Specifically, we will address methods for multidimensional data, and strategies for avoiding/handling dropout. The course will include illustrations of specific concepts using data from two trials: one with a life-threatening disease and the second with a chronic condition.

Students will be expected to participate by suggesting solutions to a hypothetical trial designed to illustrate the concepts. Handouts will include a reference list for additional study.

After completing this workshop, participants will be able to:

1. Participate in the development of studies incorporating HRQOL assessments.
2. Develop well-defined goals and objectives for studies incorporating HRQOL.
3. Discuss the advantages and disadvantages of a number of strategies for handling multiple endpoints and missing data.

Session F 🕮

The Design and Analysis of Non-inferiority Trials

Speaker: Dr. Brian Wiens, Alcon Laboratories

Moderator: Xiaoming Li

There are many factors and pitfalls involving the design, analysis, and conduct of non-inferiority trials. This presentation discusses the various issues involved with non-inferiority trials. Specific topics include

- Ethical Use of Placebo
- Constancy of Effect
- Effect Modification
- Margin Determination
- Assay Sensitivity
- Biocreep
- Evaluating the active control effect
- Regression to the mean and related biases
- Across trials inference
- Surrogate hypotheses
- Methods of Analysis
- Error Rate Control
- Trial Conduct and Blinding
- Strength of Evidence and Reproducibility
- Three arm non-inferiority trials
- Multiple testing of superiority and non-inferiority hypotheses

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

1:00 - 4:00 PM

Session G

Statisticians and Metabolomics: Collaborative Possibilities for the Next *omics Revolution

Speaker: Professor David Banks, Duke University

Moderator: Alfred H. Balch

Metabolomics is a new area in bioinformatics that uses estimates of metabolite abundance to determine disease status, assess risks associated with prospective drug therapies, and understand human biochemical processes. Although similar in many ways to proteomics, it provides both fresh statistical challenges and important scientific opportunities. Main problem areas are to:

1- Make strong use of the additional information that is available from our greater knowledge of the human metabolome (as compared to the proteome).

2- Develop data mining procedures tuned to this kind of data.

3- Create experimental designs that support cross-platform experiments, calibration, and quality control.

But the scientific opportunities are commensurate with the challenge---in particular, the domain knowledge that exists on the chemical structure of metabolites and the pathways that produce them can eliminate much of the uncertainty that arises in proteomics. This tutorial details the measurement process, and then summarizes current work on quality control, measurement calibration, denoising, peak extraction, and data mining. There are specific recommendations, drawn from experience with a private company that performs metabolomic analyses, as well as a detailed discussion of two case studies regarding ALS disease and preterm labor.

Session H

Emerging Challenges to Clinical Trial Methodology

Speaker: Dr. H.M. James Hung, US Food and Drug Administration

Moderator: Ivan Chan

In the last decade, the clinical trial methodology involved in regulatory applications is increasingly complex. As the awareness of potential ethical issues with use of placebo increases, an active control is increasingly considered as a comparative arm for assessing the effect of a test treatment. Non-inferiority trial design has therefore been revisited. On another front, even for the placebo-controlled trial, the conventional standard design has been faced with many challenges aiming at design adaptability, following the invention of group sequential designs. Evidential standard promotes consideration of more innovative trial designs and inferential frameworks for studying more than one objective or endpoint in regulatory submissions. This tutorial will discuss some emerging challenges in the following topics:

1. Active controlled trial design
   - Non-inferiority trial with a placebo arm
   - Non-inferiority trial without a placebo arm
   - Approaches to define non-inferiority margin
   - Intent-to-treat versus per-protocol versus on-treatment analysis
   - Testing for superiority and non-inferiority
2. Adaptive design
   - Sample size re-estimation
   - Adaptive selection
3. Multiple comparison considerations
   - Primary endpoint family versus secondary endpoint family
   - Composite endpoint
4. Roles of modeling and simulation
   - Early phase trial
   - Pivotal trial
5. Multi-regional clinical trials
   - Analysis consideration
   - Design consideration

Wednesday December 8, 2010 8:30 – 11:30 AM

Session I
Benefit:Risk Assessment, Subgroup Analyses, and Prediction for Interim Data Monitoring
Speaker: Prof. Scott Evans, Harvard School of Public Health
Moderator: Naitee Ting

The monitoring and evaluation of benefit:risk is a fundamental element of clinical trials and drug, biologic, and device development. Regulators weigh the benefits and risks when evaluating drugs for approval, sponsors assess the benefit:risk profile of their drugs to aid development decisions, and data monitoring committees make recommendations regarding study conduct based on benefit:risk assessment during interim data analyses. Despite benefit:risk assessment lying at the heart of the development process, there is a need for a more systematic, creative, and informative approaches to evaluation. We discuss the challenges to benefit: risk assessment, evaluate elements of trial design and conduct that affect benefit:risk evaluation, present methods for analyses including within-patient analyses and potential for personalized medicine, and present ideas for reporting benefit:risk analyses. We discuss keys to improved benefit:risk assessment with detailed interactions between statisticians, clinicians, and other researchers. Subgroup analyses are commonly utilized in clinical trials to assess whether treatment effects are homogenous across subsets of subjects defined by baseline characteristics. However, subgroup analyses introduce analytic challenges and can lead to overstated and misleading results. How to conduct subgroup analyses and how to interpret and report subgroup analysis results using examples drawn from recent medical literature will be covered. We will discuss new methods to identify subgroups that will benefit from treatment or be at substantial risk for toxicity.

Interim analyses of clinical trials are frequently conducted to evaluate efficacy and/or futility. Existing methods such as group sequential methods are useful but provide limited information regarding effect sizes (e.g., treatment differences) and none uses prediction to convey information regarding potential effect size estimates and associated precision, with trial continuation. We discuss use of prediction and predicted intervals as a flexible and practical tool to aid in decision-making during interim analyses

Session J 🕮
Monte Carlo Simulation for the Pharmaceutical Industry: Concepts, Algorithms, and Case Studies
Dr. Mark Chang, Amag Pharmaceuticals
Moderator: Wenjin Wang

Drug development, aiming at improving people's health, becomes more costly every year. The pharmaceutical industry must join its efforts with government and health professions to seek new, innovative, and cost-effective approaches in the development process. During this evolutionary process in the next decades, computer simulations will no doubt play a critical role. Computer simulation or Monte Carlo is the technique of simulating a dynamic system or process using a computer program.

An overview of Monte Carlo simulations in the pharmaceutical industry, including clinical trial simulation, dynamic drug supply simulation, prescription drug commercialization, Molecular design and simulation, disease modeling & biological pathway simulation, pharmacokinetic and Pharmacodynamic simulations will be given. Focus is on basic simulation concepts, methods & applications in clinical trials. Topics will include random number generation, game & decision theory, Markov decision process, adaptive trial simulation, clinical development program optimization & portfolio prioritization. Various practical simulation models will be discussed. Attendees will learn the overall landscape of Monte Carlo Simulations in the pharmaceutical industry and basic simulation techniques are necessary to carryout simulation effectively and avoid ad hoc approaches.

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

Session K 🕮
Clinical Trial Methodology: Case Studies
Dr. Karl E. Peace, Georgia Southern University
Moderator: Kalyan Ghosh

A clinical trial is a research study conducted to assess the utility of an intervention in volunteers. Interventions may be diagnostic, preventative or treatment in nature and may include drugs, biologics, medical devices or methods of screening. Interventions may also include procedures whose aim is to improve quality of life or to better understand how the intervention works in volunteers. Clinical trial methodology (CTM) comprises all methods required for the protection of participants in a clinical trial and all methods necessary to provide a valid inference about the objective of the trial. In short, CTM consists of all methods necessary to develop and conduct a quality clinical trial protocol and to provide quality data collection, biostatistical analyses and a clinical study report while maintaining the highest standards of ethics and excellence. Several landmark clinical trials from the presenter's own experience that led to regulatory approval of drugs (e.g. reducing CHD risk, optimal treatment of DU, prevention of GU, and a parallel bioequivalence trial) will be reviewed from a case study approach with attention to CTM utilized

Session L
What Drug Development and The Medical Community Could Learn From Sports
Dr. Scott Berry, Berry Consultants
Moderator: Ivan Chan

There are many statistical concepts, fallacies, and myths that are misunderstood in the medical community. Many of these same concepts are also misunderstood in the sports world. A reason for such a low rate of phase III success is the same reason poor contracts are given to free agents. Trying to compare two drugs that have never been in the same clinical trial is the same problem as comparing Babe Ruth and Barry Bonds--their careers never overlapped. A recent JAMA publication (Bassler, et al) makes fundamental errors in their conclusions -- the same errors commonly made by sports commentators. Some of the concepts that will be explored in depth, with examples of each from medical research and sports, will be

a) Variability: The difference between truths and data
b) Multiplicities: Still the most misunderstood and abused statistical concept in both biostatistics and sports
c) Regression-To-The-Mean: A simple, yet incredibly powerful concept that is rarely understood
d) Conditioning Fallacies: How the law-of-averages is often abused
e) Causation: While sports has less understanding of this idea than the medical community; there are still examples of mistakes.

Other topics such as meta-analysis, decision analysis, and the role of modeling and simulation will be discussed.

TWO SIMULTANEOUS SHORT COURSES
THURSDAY AND FRIDAY, DECEMBER 9-10, 2010

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

SAS for Mixed Models: Applications for Repeated Measures, Generalized Linear Mixed Models, and Sample Size Computation 🕮

Instructors: Ramon Littell, University of Florida
Walter W. Stroup, University of Nebraska
Moderator: Alfred H. Balch

Text: *SAS for Mixed Models, 2nd ed.*

This course surveys mixed model methods for designed experiments, focusing on experiments with various forms of clustering, including repeated measures, split-plot and multi-location studies. It covers mixed models for normally distributed data as well as generalized linear mixed models for non-normal data (e.g. proportions and counts. The course will include use of mixed model methods for planning; design and sample size determination as well as data analysis. Planning and design are especially important because much of the conventional wisdom about design follows from normal theory; designs well suited for normally distributed data are often poorly suited for non-normal data. Examples use SAS procedures, mostly MIXED and GLIMMIX. Attendees need a background in design and analysis of experiments.

- **Basics of statistical models**
  - How the model equation $y = X\beta + Z\mu + \varepsilon$ arises and why it is appropriate for normal data only
  - Probability model: $y \sim (\mu, \Sigma)$; link: $\eta = g(\mu)$; linear predictor: $\eta = X\beta + Z\mu$ - how it arises & why it is essential for GLMM
- **Essential Background**
  - Linear Mixed Models (normal case)
  - Generalized Linear Mixed Models
  - Estimation and Inference Basics
- **Mixed Model Issues**
  - Multiple Error Terms
  - Satterthwaite
  - Correlated Errors and Repeated Measures
    - Why it's an issue
    - How to choose covariance model
  - Inference Space and Best Linear Unbiased Predictions (BLUPs)
  - Testing Variance/Covariance components (COVTEST in GLIMMIX)
- **GLMM Issues**
  - Counts
    - Overdispersion
    - Poisson, Negative Binomial, etc
    - Zero-inflated models
  - Rates and Proportions
    - Binomial: logit & probit models
    - Beta
  - Repeated Measures in GLMMs
    - R-side (working correlation/GEE) vs. G-side (conditional/GLMM) models
    - Choosing among competing models
  - Planning
    - Theory allowing use of MIXED/GLIMMIX to compute power
    - Example with normal data: choose between complete block, BIB, split-plot – same sample size, power characteristics very different
    - Multi-location binomial example
    - Count data example

Ramon C. Littell is Professor Emeritus of Statistics at the University of Florida, where he taught, conducted research, and consulted in the Institute of Food and Agricultural Sciences for nearly 40 years. He is presently a Consulting Associate at Info TECH, Inc. in Gainesville, FL. He is author or coauthor of about 150 articles in various scientific journals, and coauthor of four books on using SAS for statistical applications. He is an ASA Fellow and has received other awards for applications of statistics and service to the profession. His main interest is in mixed linear models

Walt Stroup is Professor and Chair, Statistics Department; University of Nebraska. Besides the text, he authored *SAS for Linear Models, 4th ed.* He has conducted numerous short courses worldwide on mixed and generalized linear models for industry and professional organizations. He is an ASA Fellow and was honored with Product Quality Research Institute's 2009 Excellence in Research award..

Bayesian Adaptive Methods for Clinical Trials 🕮

Instructors: Brad Carlin, University of Minnesota
Scott Berry, Berry Consultants
Moderator: Ivan Chan

Text *Bayesian Adaptive Methods for Clinical Trials*

Thanks in large part to the rapid development of Markov chain Monte Carlo (MCMC) methods and software for their implementation; Bayesian methods have become ubiquitous in modern biostatistical analysis. Statisticians working in medical device and early phase drug research (especially Phase I oncology trials) have long appreciated adaptive Bayes methods' ability to get good answers quickly.

This two-day course introduces Bayesian methods, computing, and software, and then goes on to elucidate their use in Phase I, II, and III trials. We include descriptions of how the methods can be implemented in various stand-alone packages as well as our own code written in R, WinBUGS, and BRugs. In particular, we will illustrate the different ways a Bayesian might think about power when designing a trial, and how a Bayesian procedure may be calibrated to guarantee good long-run frequentist performance (i.e., low Type I and II error rates), a subject of keen interest to the FDA.

Day 1, Morning: Intro to Hierarchical Bayes Methods and Computing

Bayesian inference: point and interval estimation, model choice; Bayesian computing: MCMC methods, Gibbs sampler, Metropolis-Hastings algorithm; Hierarchical modeling and metaanalysis; Principles of Bayesian clinical trial design: predictive probability, indifference zone, Bayesian and frequentist operating characteristics (power, Type I error).

Day 1, Afternoon: Bayesian design and analysis for Phase I studies

Rule-based designs for determining the MTD (e.g., 3+3); Model-based designs for determining the MTD: CRM, EWOC, TITE monitoring, toxicity intervals; Efficacy versus toxicity; Combination therapy; Examples and software.

Day 2, Morning: Bayesian design and analysis for Phase II studies

Standard designs: Phase IIA (single-arm) vs. Phase IIB (multi-arm); Predictive probability-based methods; Sequential stopping: for futility, efficacy; Adaptive randomization and dose allocation; Dose ranging and optimal biologic dosing; Hierarchical Phase II models and examples; Decision-theoretic methods.

Day 2, Afternoon: Bayesian design and analysis for Phase III studies

Confirmatory trials; Adaptive confirmatory trials: adaptive sample size, futility analysis, arm dropping; Modeling and prediction; Examples from FDA-regulated trials; Seamless Phase II-III trials; Incorporating historical data; Equivalence studies; Multiplicity/subgroup analysis; Summary and discussion.

Students are encouraged to bring laptops with the latest versions of WinBUGS and R installed from www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml and www.r-project.org, respectively. The presentation will assume familiarity with basic Bayesian methods and MCMC algorithms, at the level of, say, Chapters 2 and 3 of Carlin and Louis (2009) or Chapters 2, 3, 5 and 11 of Gelman et al. (2004).

Brad Carlin is Mayo Professor of Public Health, and Professor and Head of Biostatistics in the School of Public Health at the University of Minnesota. In addition to his three textbooks, he is author of over 115 papers in refereed books and journals. He was the 2000 winner of the American Public Health Association's Mortimer Spiegelman Award, and served for three years as editor-in-chief of *Bayesian Analysis*, the official journal of the International Society for Bayesian Analysis (ISBA).

Scott M. Berry is President and Statistical Scientist at Berry Consultants. Since 2000 he has been involved in the design of more than 50 Bayesian adaptive clinical trials for pharmaceutical and medical device companies. His research interests are in Bayesian methods in clinical trials, adaptive clinical trials, Bayesian computation, and hierarchical models. He is also a renowned sports statistician, with over 40 articles on sports statistics, ranging from *JASA* to *ESPN the Magazine*. He received his PhD from Carnegie Mellon University and spent 5 years as a member of the statistics faculty at Texas A&M University.

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 5th, 7:30 AM December 6th through December 8th and 8 AM on December 9th. Checks and, **if absolutely necessary**, this form should be mailed to Manoj Patel; 114 Doric Court; Cary, NC 27519

Last Name: _____ First Name: _____ Mr. ❑ Ms. ❑ Mrs. ❑ Dr. ❑ Other ❑

Organization Name: _____ Mailing Address: _____

City: _____ State: _____ Zip: _____

Daytime Telephone: _____ Facsimile: _____ E-mail: _____

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

Conference Registration	Payment Must Be Made or Check Mailed On or Before October 1st	November 1st	Later or Onsite	Amount
Three Day Conference	$550	$670	$800	_____
One Day Registration, Monday, Tuesday, or Wednesday (circle 1)	$275	$325	$380	_____
Student (Proof of full time college status needed) or Retiree	$225	$275	$325	_____
One-Hour Registrant Reception with cold drinks and snacks Sunday 6:30 PM	**Free**		**Check box**	❑
Speaker Dinner, Monday 7:00 PM	45	$50	60	_____
Short Course Registration:				
❑ **SAS for Mixed Models: Applications for Repeated Measures**	$740	$850	$970	_____
❑ **Bayesian Adaptive Methods for Clinical Trials**	$740	$850	$970	_____

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

Havana Tower Rate: ($79 + 14% Tax, and a $10 Resort Fee) $100.06 Per Room Per Night

Arrival December _____ Departure December: ___ Smoking? Circle Yes or No King? ❑ or 2 Queen Beds? ❑

Rooms Must Be Reserved With this Form or on our Web Site on or Before November 21st to Get the Conference Rate

Tropicana Room Reservation (One Night Deposit of $100.06) Hotel Cancellation Policy: 2 Days Prior to Arrival _____

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

Book Author(s) and Title Onsite availability of books cannot be guaranteed unless you place an order in advance.	# Page	Year	ISBN 13 978-	Price ($) List	Price ($) Our	# of Copy	Total ($)
Taylor and Francis							
Berry, Scott; Carlin, Bradley; Lee, J Jack; and Muller, Peter; Bayesian Adaptive Methods for Clinical Trials	312	2010	1-439-82548-8	90	57		
Chang, Mark; Monte Carlo Simulation for the Pharmaceutical Industry: Concepts, Algorithms, and Case Studies	552	2010	1-439-83592-0	90	57		
Dmitrienko, Alex; Tamhane, Ajit; and Bretz, Frank; Multiple Testing Problems in Pharmaceutical Statistics	320	2009	1-584-88984-7	90	57		
Fairclough, Diane; Design and Analysis of Quality of Life Studies in Clinical Trials, Second Edition	424	2010	1-420-06117-8	90	57		
Hsu, Jason; Multiple Comparisons: Theory and Methods	296	1996	0-412-98281-1	110	69		
Peace, Karl; and Chen, Din; Clinical Trial Methodology	420	2010	1-584-88917-5	90	57		
Peace, Karl; Design and Analysis of Clinical Trials with Time-to-Event Endpoints	616	2009	1-420-06639-5	100	63		
Rothmann, Mark; Chan, Ivan; and Wiens, Brian; Design and Analysis of Non-Inferiority Trials	320	2010	1-584-88804-8	90	57		
Tang, Wan; He, Hua; and Tu, Xin; Applied Categorical and Count Data Analysis	360	2010	1-439-80624-1	90	57		
SAS Publishing							
Littell, Ramon; Milliken, George; Stroup, Walter; Wolfinger, Russell; Schabenberber, Oliver; SAS for Mixed Models 2nd Edition	840	2006	1-590-47500-3	90	62		

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

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

E-Mail Cancellations sent to registration@demingconference.com will be accepted until November 19th for a separate $50 fee for both the conference and courses. Afterwards, there will be no refunds but substitution of another registrant is permissible. If a registrant cancels, his or her ordered books would be mailed.

Credit Card Type: ❑ American Express ❑ Master Card ❑ Visa (Discover and other credit cards are not accepted)

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

Card Holder Signature: _____

TRAVEL TO THE CONFERENCE

AIR: Check both Atlantic City (ACY) and Philadelphia (PHL) to search for the best fare and connections. The cheapest quick airport connection is the Tropiana shuttle, requiring reservations at 1-800-559-2040 or fax them at 1-215-616-5380. It meets all flights and charges $13 from ACY (cab is $27+) and $45 from PHL directly to the Tropicana. A tip is expected. The cheapest connection from PHL is the below referenced SEPTA, but this will take more than two hours. One can rent a car (www.bnm.com) but it isn't necessary during one's stay. Also consider discount airlines not on the major search engines such as WestJet, westjet.com (from Toronto) and Spirit, www.spiritair.com to ACY; and AirTran www.airtran.com (also to ACY), Frontier www.frontierairlines.com, Southwest, www.southwest.com, and USA 3000, www.usa3000airlines.com to PHL. These airlines offer the additional advantage that they sell one-way tickets without a premium that is useful if one is using the conference as a stopover. While we don't recommend Newark Airport, there is a #67 NJ Transit bus (requiring a change at Toms River) as well as several train service options to Atlantic City. The whole trip would take about three hours as opposed to about ninety minutes if one rented a car.

RAIL: NJ Transit has relatively frequent local (14 daily trips with 6 stops) service to Philadelphia connecting with Amtrak, NJ Transit to NYC, and SEPTA at 30th Street and PATCO at Lindenwold. Free shuttle busses meet all trains and provide direct service to the Tropicana. www.njtransit.com/pdf/rail/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 $2.25 jitney on Pacific Avenue to quickly get to the Tropicana. Greyhound has service directly to the Tropicana with a coin rebate, and a four-day open return from Philadelphia, NYC, Baltimore and Washington with details on www.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 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 paying $5 extra for 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 tropicana.net/images/QtrDisplayMap_20080222_final.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. 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, 2011. The award will be announced and paid directly to the applicant on May 15, 2011. 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 2011 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-one consecutive years.**