Short Courses for ICSA Applied Statistics Symposium,
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Multiple Comparisons in Clinical Trials

H.M. James Hung and Sue-Jane Wang
US Food and Drug Administration

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

1. Early phase learning trials
2. Single versus multiple confirmatory placebo-controlled trials
   - Multiple endpoints
   - Multiple doses
   - Multiple analyses
3. Active-controlled trials
   - Placebo is present
   - Placebo is absent
   - Non-inferiority and superiority analyses
4. Adaptive design trials
   - Early phase trial
   - Pivotal trial

Short Course Instructors:

H.M. James Hung, PhD
Director, Division of Biometrics I, OB/OTS, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue, Bldg 21 Room 4616
Silver Spring, MD 20993-0002
Tel: (301)-796-1092
Fax: (301)-847-8525
E-mail: hsienming.hung@fda.hhs.gov

Sue-Jane Wang, PhD
Associate Director, Office of Biostatistics, OTS, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue, Bldg 21 Room 3562
Silver Spring, MD 20993-0002
Tel: (301)-796-0831
Fax: (301)-796-9734
E-mail: suejane.wang@fda.hhs.gov

About the Instructors

Dr. H.M. James Hung is Director of Division of Biometrics I, Office of Biostatistics, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA). He is an author of over 90 papers and book chapters in statistical and medical literature. His research interests include factorial design clinical trials, utility of p-value distribution, adaptive design/analysis in clinical trials, and non-inferiority trials, multi-regional clinical trials. He made major contributions to regulatory reviews of many large mortality or morbidity clinical trials in cardiovascular and renal disease areas. He has presented over 180 invited talks and short courses in his research areas. Dr. Hung received two FDA/CDER Scientific Achievement Awards, one FDA Scientific Achievement Group Award and many other awards for the recognition of his scientific contributions to the US FDA. Currently, he serves as an Editor-in-Chief for Journal of Pharmaceutical Statistics and an Associate Editor for Statistics in Medicine and Journal of Biopharmaceutical Statistics. He is a Fellow of the American Statistical Association and an elected member of the International Statistical Institute.

Dr. Sue-Jane Wang is Associate Director for Pharmacogenomics and Adaptive Design, Office of Biostatistics, Office of Translational Sciences, CDER, FDA. Dr. Wang is an author of over 90 papers and book chapters in statistical, clinical, genetic, bioinformatics, and pharmacogenomics literature. She made major contributions to regulatory reviews in these areas. As a result, Dr. Wang received two FDA Outstanding Intercenter Scientific Collaboration Awards and was recently awarded the FDA level Scientific Achievement individual Awards in recognition of her sustained record of published regulatory research in statistical design and methodology advancing complex and emerging clinical trial designs and analysis that support regulatory guidance, policies and review. She has presented over 200 invited talks, discussion, and short courses in her research areas including non-inferiority, multi-regional trials. She is an elected member of the International Statistical Institute. She has served as an Editor-in-Chief for Pharmaceutical Statistics, and is an Associate Editor for Statistics in Medicine and Statistics in Biosciences. She is conference co-chair for MCP 2011 conference.

Design and Analysis of Cross-over Trials

Byron Jones
Pfizer

(including new material that will appear in the 3rd edition of my book with Mike Kenward, due out late 2011/early 2012)

About the Instructors

Byron Jones joined Pfizer Ltd in 2004, having spent the previous four-and-half years in a similar role at GSK. Before that he was a university professor and consultant to the pharmaceutical industry. Byron is a Fellow of both the American Statistical Association and the Royal Statistical Society. He has over 100 publications in peer-reviewed journals and has co-authored four books, including "The Design and Analysis of Cross-over Trials, Second Edition", with Michael Kenward, and "Bioequivalence and Statistics in Clinical Pharmacology", with Scott Patterson, both of which are published by CRC Press/Chapman and Hall. Byron was a founding Editor-in-Chief of the journal Pharmaceutical Statistics and previously was the Regional Editor of the Journal of Biopharmaceutical Statistics. Byron is still active in research and retains close ties with Academia. He currently holds Honorary Professorships at University College London and at the London School of Hygiene and Tropical Medicine. He is a member of several university advisory boards, including one at Oxford University. At Pfizer he provides statistical advice and training to colleagues all over the globe.

Basic Concepts in Equivalence/Noninferiority Testing: Issues and Challenges

Tie-Hua Ng
US Food and Drug Administration

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 short course 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. This NI margin is closely related to M_1 and M_2, the NI margins discussed in the FDA draft guidance on NI clinical trials issued in March of 2010.

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.

About the Instructors

Dr. Ng received his Ph. D. Degree in Statistics in 1980 from the University of Iowa. He held several positions before joining the US Food and Drug Administration (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 interest includes equivalence/noninferiority testing and Bayesian approach.

Over the past 18 years, he had made numerous presentations at professional meetings and published extensively in the area of active controlled/noninferiority studies. More specifically, his research focused on the determination of noninferiority (NI) margin and issues of simultaneous testing of NI and superiority. He first proposed that the NI margin should be a small fraction of the therapeutic effect of the active control as compared to placebo in his 1993 paper published in the *Drug Information Journal*. Subsequently, two follow-up papers were published --- one in the *Drug Information Journal* in 2001 and other one in *Statistics in Medicine* in 2008. He raised the issues of simultaneous testing of NI and superiority in two of his papers published in the *Journal of Biopharmaceutical Statistics* in 2003 and 2007.

Group Sequential Methods in Clinical Trials

K. K. Gordon Lan
Johnson & Johnson Pharmaceutical Research and Development

About the Instructors

Senior Director, Johnson & Johnson PRD

K. K. Gordon Lan received his Ph.D. in Mathematical Statistics from Columbia University in 1974. Before joining Johnson & Johnson in 2005 as Senior Director of Statistical Science, he held positions as Mathematical Statistician at the National Heart, Lung and Blood Institute (NHLBI/NIH), Professor of Statistics at George Washington University, Distinguished Scientist at Pfizer and Statistics Fellow at Sanofi-Aventis.

Gordon has published more than 50 research papers in professional journals and has given more than 200 invited talks at universities and professional meetings. He is interested in statistical methods for clinical trial design and data analysis. Gordon was elected Fellow of the American Statistical Association in 1992 and Fellow of the Society for Clinical Trials in 2009.

Dose Finding Studies: Methods and Implementation

Frank Bretz and José Pinheiro
Novartis Pharma AG
Johnson & Johnson Pharmaceutical Research and Development

Despite revolutionary advances in basic biomedical science, the number of new drug applications has been declining over the past several years. In response, different initiatives, such as the Critical Path Initiative, have been put in place to identify and propose ways to address the key drivers behind this pharmaceutical industry pipeline problem,. One well-known cause is poor dose selection for confirmatory trials resulting from inappropriate knowledge of dose response relationship (efficacy and safety) at the end of Phase II.

This course will discuss the key statistical issues leading to the problems currently observed in dose finding studies, including a review of basic multiple comparisons and modeling methods, as traditionally used in these studies. A unified strategy for designing and analyzing dose finding studies, denoted MCP-Mod, combining multiple comparison and modeling, will be the major focus of the course. It will be discussed in detail, including a step-by-step description of its practical implementation. Case studies based on real clinical trials, together with software implemented in R, will be used to illustrate the use of the methodology. A practical motivated by a real dose finding study will allow attendees to get hands-on experience with the methods and the R software.

About the Instructors

Dr. Frank Bretz received his Ph.D. in Statistics from the University of Hannover, Germany, in 1999. Afterwards, he worked for one year as biostatistician at Byk Gulden Pharmaceuticals, Konstanz, in the design and analysis of clinical trials. He then moved back to the University of Hannover as Assistant Professor. Frank finished in 2004 his

post-doctoral thesis ("Habilitation") at the Medical University of Hannover and joined in the same year the Statistical Methodology group at Novartis Parma, where is currently a Biometrical Fellow. He has supported the methodological development in various areas of drug development, including dose-finding, multiple comparisons, and adaptive designs. Since 2007 he is an Adjunct Professor at the Medical University of Hannover. Dr. Bretz is a core member of the PhRMA working group on "Adaptive Dose-Ranging Designs". Since 2002 he is the treasurer of the German Region of the International Biometric Society. From 2004 until 2007 he was the head of the working group on "Statistical Methods in Bioinformatics" of the German Region / IBS. He is a co-developer of the *multcomp* software in R for multiple comparison procedures in general linear models. He has authored or co-authored more than 50 articles in peer-reviewed journals and one book.

Dr. José Pinheiro is a Senior Director in the Adaptive Designs group at Johnson & Johnson PRD. Prior to that he worked at Novartis Pharmaceuticals for eight years, most recently as a Senior Biometrical. He has been involved in the development and implementation of innovative statistical methods for early and late phase clinical trials across a wide range of therapeutic areas, such as oncology, neurosystems, cardiovascular, transplantation, respiratory diseases, and dermatology. He received his Ph.D. in Statistics from the University of Wisconsin – Madison in 1994 and did postdoctoral work for two years in the Biostatistics department at the same university. He is a past-chair of the Statistical Computing Section of ASA, having also served as chair of the Awards Committee for the same section. Since 2005, Dr. Pinheiro has served as a co-leader of the PhRMA PISC working group on Adaptive Dose Ranging Studies and participated in the PhRMA PISC working group on Adaptive Designs. He is the vice-chair of the Biostatistics and Data Management Technical Group. He was the co-chair for the 2006 ENAR meeting of the International Biometric Society, having also served as Secretary of ENAR. He is an associated editor for the Biometrical Journal, Statistics in Biopharmaceutical Research, and Statistics in Biosciences. The author of a book on and the most widely used software in S-PLUS and R for mixed-effects models, eight book chapters, and over 50 refereed papers, Dr. Pinheiro has presented over 20 short courses and given over 80 invited presentations at conferences, government agencies, and universities around the world.

Strategies for Extracting Reliable Information from Megavariate Data

Dhammika Amaratunga
Johnson & Johnson Pharmaceutical Research and Development

A spate of recent advances in genomics has significantly altered the way research is being conducted in biology and medicine. It is now possible to investigate the behavior of genes and proteins thousands at a time, a powerful resource for the biological researcher. Of the current technologies, the most prominent is the DNA microarray, which can be used to profile the expression patterns of tens of thousands of genes simultaneously. How

to properly analyze and interpret the enormous amounts of data this type of technology generates remains a challenge as its high dimensional (megavariate) structure, comprising many variables but few samples, renders it vulnerable to over-fitting and over-interpretation. Development of methodology for analyzing megavariate data remains a work in progress but new techniques have been developed that are worthy of consideration. Ultimately, a multi-faceted approach is likely to be the most effective at extracting reliable information. For instance, for a standard well-designed comparative microarray experiment, a fairly rigorous prescription for determining a gene expression signature would include (1) a quality control step to settle any anomalies in the data and to ensure that the data indeed carry a signal, (2) an individual gene analysis to identify differentially expressed genes using a method that borrows strength across genes in a nonparametric way to increase efficiency, (3) an analysis of gene sets to identify affected biological processes and pathways, (4) an ensemble classification procedure to identify similarities and/or dissimilarities amongst the samples and the genes associated with any dissimilarities, (5) a procedure to integrate concomitant data to assess concurrence of findings. This course will introduce the issues underlying megavariate data analysis and will use actual case studies to review this multi-faceted approach.

About the Instructors

Dhammika Amaratunga is Senior Research Fellow in Nonclinical Biostatistics at Johnson & Johnson Pharmaceutical Research & Development. He has been involved in microarray data analysis since 1997, the early days of microarrays. He and his team have numerous publications, including a book, and they have also given numerous presentations and courses on this topic. He has also 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. He is a Fellow of the American Statistical Association. He has a B.Sc. from the University of Colombo, Sri Lanka, and a Ph.D. in Statistics from Princeton University, where he learnt the importance of careful exploratory data analysis while working under the supervision of John Tukey.

Design and Analysis of Group Sequential Trials: Recent Advances and Software

Mei-Chiung Shih and Balasubramanian Narasimhan,
Stanford University
Florida State University

Group sequential designs that have provisions for data monitoring and interim analyses are now widely used in confirmatory Phase III trials, especially those with survival endpoints. The past decade witnessed important methodological advances in the design of group sequential trials and in the primary and secondary analyses of the data following a

group sequential trial. The course gives an introduction to these advances and to open-source software packages available at the Center for Innovative Study Design website at the School of Medicine at Stanford University. It also provides an overview of related chapters in the monograph *Sequential Experimentation in Clinical Trials: Design and Analysis*, by Jay Bartroff, Tze Leung Lai and Mei-Chiung Shih, Springer, 2011.

About the Instructors

Mei-Chiung Shih, Ph.D. (Stanford University)
Mei-Chiung.Shih@va.gov
Balasubramanian Narasimhan, Ph.D. (Florida State University)

Using Replication Methods to Analyze Survey Data in SAS Software - Continuing Education

Anthony An
SAS Institute Inc.

Increasingly, statisticians analyze data that come from probability-based sample surveys. This requires taking into account sample design to make statistically valid inference about the study population. Previously, SAS/STAT procedures designed for survey analysis used Taylor series expansion methods for variance estimation. Beginning with the 9.2 release, SAS software offers replication methods for variance estimation, including balanced repeated replication (BRR) and the jackknife. In this workshop, you will learn how to analyze survey data and perform variance estimation in the SURVEYFREQ, SURVEYLOGISTIC, SURVEYMEANS, and SURVEYREG procedures using the jackknife, BRR, and Fay's BRR method. You will also learn how to create appropriate replicate weights and estimate the variance for survey data when you have been supplied with a set of replicate weights. We will also discuss other variance estimation issues related to replication methods. The course is intended for a broad audience of statisticians who are interested in analyzing sample survey data. Familiarity with basic statistics, including regression analysis, is required.