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

Sponsored by
Deming Conference Organization
International Chinese Statistical Association
AMERICAN STATISTICAL ASSOCIATION: Biopharmaceutical Section

Three-Day Conference, December 6 – December 8, 2021
One Short Course, December 9 - 10, 2021

Virtual Conference
All Times in the Schedule are U.S. EST Time

Three Keynotes on December 6-8, 2021

Keynote 1: What is Translational Biostatistics and How to Implement It? Prof. **L. J. Wei**, Harvard University
Keynote 2: Multiple Imputation and Missing Data, Prof. **Stef van Buuren**, University of Utrecht, Holland
Keynote 3: Two Key Ideas in Missing Data – Missing at Random and Response Propensity, Prof. **Rod Little**, University of Michigan

Twelve Sessions of Tutorials on December 6-8, 2021 and One Short Course on December 9-10, 2021

Short Course: Estimands, Missing Data Handling, and Bayesian Methods for Clinical Trials, **Frank Liu**, Merck & Co. Inc and **Fang Chen**, SAS® Institute

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

The 3-day Deming Conference on Applied Statistics provides a learning experience on recent developments in statistical methodologies in biopharmaceutical applications. The 77th Annual Deming Conference will be held virtually on December 6-14, 2021. There will be two parallel half-day tutorial sessions based on recently published books for the first three days for a total of 12 tutorial sessions (December 6-8). Then the conference will continue with a 2-day short course on December 9 and 10. The books used for the tutorial sessions and for the short course as well as books written by invited speakers will be sold at appreciable discounted prices. The books are not included in the tutorial sessions or short course registration. Registrants are responsible to purchase the book individually.

All registration will be done electronically online. The 3-day conference starts with keynote talks at 11:00 am. The short course also starts at 11:00 am. An email will be sent registrants on November 15th with links to participate the virtual conference.

THREE-DAY REGISTRANTS WILL RECEIVE AN ELECTRONIC COPY OF THE HANDOUTS FOR ALL SESSIONS.

RECEIPTS and a CERTIFICATE OF ATTENDANCE will be distributed electronically. Register and pay for the conference online as early as possible at www.demingconference.org. This gives you an instant email acknowledgement. Payment must be paid by a credit card. E-Mail Cancellations sent to registrar@demingconference.org will be accepted until November 16th for a separate $50 fee for both the conference and courses. Afterwards, there will be no refunds, but substitution of another registrant is permissible.

There will be no Poster Session this year.

There will be student scholar presentations. Selected scholars can attend the 3-day conference without paying a registration fee. For a student scholar application, please contact Dr. Sofia Paul, Deming Scholar Chair, at sofia.x.paul@gsk.com.

Seventy-Seventh (77th) Annual Deming Conference on Applied Statistics

Virtual Conference*

Sponsored by the Biopharmaceutical Section of the ASA, International Chinese Statistical Association, and the Deming Conference Organization

Monday December 6, 2021

11 AM ⇒ 12 PM Keynote: What is Translational Biostatistics and How to Implement It? Prof. L. J. Wei, Harvard University
Moderator: Pinggao Zhang

Morning Tutorials 12 PM to 3 PM

Session A	Session B
Semiparametric Regression Analysis of Interval-Censored Data Danyu Lin, University of North Carolina @ Chapel Hill Moderator: Wenjin Wang	**Precision Gains in Randomized Studies Using Covariate Adjustment With Ordinal and Time-To-Event Endpoints** Iván Díaz, Cornell University Moderator: Kalyan Ghosh

Break followed by Afternoon Tutorials 3:30 PM to 6:30 PM

Session C	Session D
Group Sequential Design (GSDESIGN) and Non-Proportional Hazard Keaven Anderson, Yilong Zhang and Xiao Nan, Merck & Co. Inc Moderator: Bill Wang	**Marginal Models in Analysis of Correlated Binary Data with Time-Dependent Covariates in Biomedical Clinical Trials** 🕮 Jeffrey R. Wilson and Ding-Geng Chen, Arizona State University Moderator: Walter R. Young

Tuesday December 7. 2021

11 AM ⇒ 12 PM Keynote: Multiple Imputation and Missing Data, Prof. Stef van Buuren, University of Utrecht, Holland
Moderator: Alfred H. Balch

Morning Tutorials 12 PM to 3 PM

Session E	Session F
Toward Better Practice of Covariate Adjustment in Analyzing Randomized Clinical Trials Shao Jun, University of Wisconsin – Madison and Ting Ye, University of Washington Moderator: Naitee Ting	**C'mon in … The DOOR is Open: Pragmatic Benefit:Risk Evaluation Using Outcomes to Analyze Patients Rather than Patients to Analyze Outcomes** Scott Evans and Toshimitsu Hamasaki, George Washington University Moderator: Bill Wang

Break followed by Afternoon Tutorials 3:30 PM to 6:30 PM

Session G	Session H
Beyond Bonferroni Correction – Innovation, Intuition and Common Sense Qian Helen Li, BMS Moderator: Naitee Ting	**Extracting Real-World Evidence from Real-World Data** Rebecca Hubbard, University of Pennsylvania and Xu Shi, University of Michigan Moderator: Kalyan Ghosh

Wednesday December 8, 2021

11 AM ⇒ 12 PM Keynote: Two Key Ideas in Missing Data – Missing at Random and Response Propensity, Prof. Rod Little, University of Michigan
Moderator Alfred H. Balch

Morning Tutorials 12 PM to 3 PM

Session I	Session J
The Treatment of Missing Data in Clinical Trials Rod Little, University of Michigan Moderator: Alfred H. Balch	**Robust Methods for Assessment of Average and Scaled Average Bioequivalence** Divan Burger, University of Pretoria, South Africa Moderator: Din Chen

Break followed by Afternoon Tutorials 3:30 PM to 6:30 PM

Session K 🕮	Session L
Using SAS PROC BGLIMM and MCMC for Bayesian Analysis of Mixed Models Walter Stroup, University of Nebraska Moderator: Alfred H. Balch	**Statistical Analyses Targeting Estimands** Frank Bretz and Dong Xi, Novartis Moderator: Ivan S F Chan

Thursday & Friday December 9-10, 2021

11:00 AM⇒12:30 PM Lecture/ 12:30 PM ⇒ 1:00 PM *Break*/ 1:00 PM⇒2:30 PM Lecture /
2:30 PM⇒ 2:50 PM *Break* / 2:50 PM⇒4:20 PM Lecture / 4:20 PM⇒4:30 PM *Break* / 4:30 PM ⇒ 6:00 PM Lecture

Short Course: Estimands, Missing Data Handling, and Bayesian Methods for Clinical Trials
Frank Liu, Merck & Co. Inc and Fang Chen, SAS® Institute Inc.
Moderator: Ivan S. F. Chan

All tutorial and short course titles, presenters and moderators from 1970 onward are on www.demingconference.org

🕮 Session is based on a recently published text that is available for a discounted price. The book used in tutorials or short courses is not included in registration. Attendees will be provided links and promotion codes to order the books themselves.

All times in the schedule refer to US EST Time

*Virtual conference information with links to participate will be sent to registrants on Nov 15th, 2020

Conference Speakers Biography

Keaven Anderson (Ph.D. in Statistics from Stanford University) is an Associate Scientific VP of Methodology Research at Merck focused on late-stage statistical design and analysis. Keaven is a Fellow of the American Statistical Association. He has a long-standing interest in methodology, including survival analysis, group sequential design and multiplicity. He is the primary author of the gsDesign R package for group sequential design. While he has extensive experience in many therapeutic areas, his focus has been in oncology for the last 10+ years.

Frank Bretz (Ph.D. in Statistics from Leibniz Universität Hannover) is a Distinguished Quantitative Research Scientist at Novartis. He has supported the methodological development in various areas of pharmaceutical statistics, including adaptive designs, dose finding, estimands, and multiple testing. He currently holds adjunct professorial positions at the Hannover Medical School (Germany) and the Medical University of Vienna (Austria). He was a member of the ICH E9(R1) Expert Working Group on 'Estimands and sensitivity analysis in clinical trials' and currently serves on the ICH E20 Expert Working Group on 'Adaptive clinical trials'. He is a Fellow of the American Statistical Association.

Divan A. Burger (Ph.D. in Mathematical Statistics from University of Free State) obtained BCom (Actuarial Science), BCom (Hons) (Mathematical Statistics) and MCom (Mathematical Statistics) degrees at the University of the Free State (UFS) in 2006, 2007 and 2009. He completed his PhD studies (2013 to 2014) under the supervision of Profs Robert Schall and Abrie van der Merwe at UFS. He previously worked at Quintiles Biostatistics in Bloemfontein (2007 to 2016) as a senior biostatistician, where he specialized in the planning, statistical analysis and reporting of clinical trial data. He was a postdoctoral research fellow at the Department of Mathematical Statistics and Actuarial Science at the University of the Free State (2015 to 2016), where his primary research areas include Bayesian mixed-effects nonlinear regression analysis. Dr Burger is currently employed at the Department of Statistics of the University of Pretoria as a senior lecturer in biostatistics and biometrics. He has published extensively in the Journal of Biopharmaceutical Statistics, Statistics in Medicine, Pharmaceutical Statistics and The Lancet.

Stef van Buuren (Ph.D. in Social Science from Utrecht University) is *Professor of Statistical Analysis of Incomplete Data* at the University of Utrecht and *Principal Scientist* at the Netherlands Organization for Applied Scientific Research TNO in Leiden. His interests include the analysis of incomplete data, child growth and development, computational statistics, measurement and individual causal effects. Van Buuren is the inventor of the *MICE algorithm* for multiple imputation of missing data. He created the *growth charts* used in the Dutch child health care system, and designed the *D-score*, a new system for expressing child development on a quantitative scale. He consults for the World Health Organization and the Bill & Melinda Gates Foundation.

(Din)Ding-Geng Chen (PhD in Statistics from University of Guelph) is the executive director and professor in Biostatistics at Arizona State University. Dr. Chen is an elected fellow of American Statistical Association (ASA), an elected member of the International Statistics Institute (ISI) and a senior expert consultant for biopharmaceuticals and government agencies with extensive expertise in clinical trial biostatistics. Dr. Chen has more than 200 referred professional publications and co-authored/co-edited 33 books on biostatistics clinical trials, biopharmaceutical statistics, interval-censored survival data analysis, meta-analysis, public health statistics, statistical causal inferences; statistical methods in big-data sciences and Monte-Carlo simulation based statistical modeling. Dr. Chen is a committee member of the Deming Conference and has been invited to give various tutorials at Deming Conference since 2011.

Iván Díaz (Ph. D. in Biostatistics from University of California at Berkeley) is an Assistant Professor of Biostatistics at Weill Cornell Medicine. He completed his Ph.D. in Biostatistics at UC Berkeley and was a postdoctoral fellow at Department of Biostatistics in The Johns Hopkins Bloomberg School of Public Health. His research focuses on the study of statistical methods for causal inference from observational and randomized studies with complex datasets. He works at the intersection of causal inference, machine learning, and mathematical statistics to develop methods that provide relevant answers to substantive questions using state-of-the-art data analysis techniques.

Scott Evans (Ph.D. in Biostatistics from University of Massachusetts) is the Director of the Statistical and Data Management Center (SDMC) for the Antibacterial Resistance Leadership Group (ARLG), His interests include the design, monitoring, analyses, and reporting of and education in clinical trials and diagnostic studies. He is the author of more than 150 peer-reviewed publications and three textbooks on clinical trials including Fundamentals for New Clinical Trialists. Professor Evans is the Editor-in-Chief of Statistical Communications in Infectious Diseases (SCID), and the Co-Editor of a Special Section of Clinical Infectious Diseases (CID) entitled Innovations in Design, Education, and Analysis (IDEA). He is the former Editor of CHANCE. Professor Evans is a recipient of the Mosteller Statistician of the Year Award, the Robert Zackin Distinguished Collaborative Statistician Award for contributions to the AIDS Clinical Trials Group (ACTG), an elected member of the International Statistical Institute (ISI), and is a Fellow of the ASA, SCT, and the Infectious Disease Society of America (IDSA).

Toshimitsu Hamasaki (Ph.D. in Engineering from Osaka University) is a Research Professor of the George Washington University (GWU) Biostatistics Center and the Department of Biostatistics and Bioinformatics. His research interests include the design, monitoring, analyses, and reporting of clinical trials. He is the author of more than 200 peer-reviewed publications and four textbooks on statistical methods in clinical trials including "Sample Size Determination in Clinical Trials with Multiple Endpoints" and "Group-Sequential Clinical Trials with Multiple Co-Objectives". Dr. Hamasaki received the Ph.D. degree in Engineering from Osaka University. Dr. Hamasaki is currently the Editor-in-Chief of Statistics in Biopharmaceutical Research (SBR), an Official Journal of the American Statistical Association (ASA). He is the co-chair of Society for Clinical Trials (SCT) 2021 Program Committee. He was the chair of ASA Committee on International Relation in Statistics and a member of the Steering Committee for the Adaptive designs CONSORT Extension (ACE) Project, an extension to the CONsolidated Standards of Reporting Trials (CONSORT) Statement for adaptive clinical trials. Dr. Hamasaki is an elected member of International Statistical Institute and a fellow of the ASA. He received the Distinguished Article Award from the Japanese Society of Computational Statistics and Hida-Mizuno Prize from the Behaviormetric Society of Japan.

Li Qian Helen (Ph.D. in Biostatistics from Harvard University) has over 20 years of experience in the field of clinical statistics and worked on a range of therapeutic areas including oncology, cardiovascular, pulmonary, pain, ophthalmic, anti-inflammatory and anti-infective drug products. Her publications cover innovative statistical methods including the area of multiplicity and survival analyses. She currently works for Bristol Myers Squibb and was an experienced statistical reviewer in FDA and NIH. She received her doctoral degree in Biostatistics from Harvard School of Public Health, had a master degree from Purdue University and undergraduate degree from Tsinghua University.

Rebecca Hubbard (Ph.D. in Biostatistics from University of Washington) is a Professor of Biostatistics in the Department of Biostatistics, Epidemiology and Informatics at the University of Pennsylvania. Her research focuses on development and application of statistical methodology for studies using data from electronic health records (EHR). This work encompasses evaluation of screening and diagnostic tests, methods for comparative-effectiveness studies, and health services research. Dr. Hubbard's methodological research emphasizes development of statistical tools to support valid inference for EHR-based analyses, accounting for complex data availability and data quality issues, and has been applied across a broad range of areas of application including oncology, neurology, and pharmacoepidemiology. Results of this work have been published in over 150 peer-reviewed papers in the statistical and medical literature. She has taught short courses at ENAR, the Summer Institutes in Statistical Genetics and Statistics for Clinical Research at the University of Washington, and for the ASA Council of Chapters for over 10 years.

Danyu Lin (Ph.D. in Biostatistics from University of Michigan) is the Dennis Gillings Distinguished Professor of Biostatistics at the University of North Carolina at Chapel Hill. Dr. Lin is an internationally recognized leader in lifetime data analysis and currently serves as an Associate Editor for Biometrika (since 1997) and JASA. He has published over 200 peer-reviewed papers, most of which appeared in top statistical journals. Several of his methods have been incorporated into major software packages, such as SAS, R and STATA, and widely used in practice. Dr. Lin received the Mortimer Spiegelman Gold Medal from the American Public Health Association in 1999 and the George W. Snedecor Award from the Committee of Presidents of Statistical Societies in 2015. Other honors include ASA and IMS Fellows, Thomson ISI's list of Highly Cited Researchers in Mathematics, JASA and JRSS(B) discussion papers, and NIH Merit Award.

Rod Little (Ph.D. in Statistics from London University) is Richard D. Remington Distinguished University Professor of Biostatistics at the University of Michigan, where he also holds appointments in the Department of Statistics and the Institute for Social Research. He chaired the Biostatistics Department at Michigan for 11 years. He has over 250 publications, notably on methods for the analysis of data with missing values and model-based survey inference, and the application of statistics to diverse scientific areas, He chaired an influential National Research Council study on the treatment of missing data in clinical trials. Little is an elected member of the International Statistical Institute, a Fellow of the American Statistical Association and the American Academy of Arts and Sciences, and a member of the National Academy of Medicine. In 2005, Little was awarded the American Statistical Association's Wilks Medal for research contributions, and he gave the President's Invited Address at the Joint Statistical Meetings. He was the COPSS Fisher Lecturer at the 2012 Joint Statistics Meetings.

Jun Shao (Ph.D. in Statistics from the University of Wisconsin–Madison) is a Professor at University of Wisconsin. He is a fellow of American Statistical Association and Institute of Mathematical Statistics. He is a former Board of Director and a former president of International Chinese Statistical Association. He is also a member of Management Board of Statistics and Its Interface. Shao Jun was the editor, coeditor, or associate

editor for many journals, including Statistical Theory and Related Fields, Journal of Nonparametric Statistics, Journal of System Science and Complexity, Statistica Sinica, Journal of American Statistical Association, Sankhya, Journal of Multivariate Analysis. He has supervised 41 Ph.D. students graduated between 1996 and 2020 and has 206 published papers in refereed journals and 7 published textbooks and research monographs.

Xu Shi (Ph.D. in Biostatics from University of Washington) is an Assistant Professor in the Department of Biostatistics at University of Michigan. Her research focuses on developing novel statistical methods that provide insights from high volume and high variability administrative healthcare data such as the electronic health records (EHR) data. She develops scalable and automated pipelines for curation and harmonization of EHR data across healthcare systems. She also develops causal inference methods that harness the full potential of EHR data to address comparative effectiveness and safety questions. She co-leads the Advanced Analytics Core of the FDA's Sentinel Initiative Innovation Center to develop innovative statistical methods to monitor the safety of FDA-regulated medical products and explore novel ways to utilize information from distributed EHR data partners.

Walt Stroup (Ph.D. in Statistics from University of Kentucky) is Emeritus Professor of Statistics at the University of Nebraska-Lincoln. He served on the University of Nebraska faculty from 1979 until 2020. His responsibilities included teaching statistical modeling, design of experiments, and research specializing in mixed models and their applications in agriculture, natural resources, medical and pharmaceutical sciences, education, and the behavioral sciences. He is the founding chair of Nebraska's Department of Statistics and served as chair from 2001 until 2010. In 2020, he received the University of Nebraska's Outstanding Teaching and Innovative Curriculum Award, the university's highest teaching honor. He was a member of PQRI's Stability Shelf-Life Working Group from its inception in 2006 until its disbanding in 2019. He received PQRI's Excellence in Research award in 2009. He co-authored SAS for Mixed Models, SAS for Linear Models, 4th ed., and authored Generalized Linear Mixed Models: Modern Concepts, Methods and Applications. He has conducted numerous short courses on mixed and generalized linear models for industry and professional organizations in Africa, Europe, Australia and North America. He is a Fellow of the American Statistical Association.

L.J. Wei (Ph.D. in Statistics from the University of Wisconsin–Madison) is a professor of Biostatistics at Harvard University. Before joining Harvard, he was a professor at University of Wisconsin, University of Michigan, and George Washington University. His main research interest is in the clinical trial methodology, especially in design, monitoring and analysis of studies. He has developed numerous novel statistical methods which are utilized in practice. He received the prestigious Wald Medal in 2009 from the American Statistical Association for his contribution to clinical trial methodology. He is a fellow of American Statistical Associating and Institute of Mathematical Statistics. In 2014, to honor his mentorship, Harvard School of Public Health established a Wei-family scholarship to support students studying biostatistics. His recent research area is concentrated on translational statistics, the personalize medicine under the risk-benefit paradigm via biomarkers and revitalizing clinical trial methodology. He has more than 220 publications and served on numerous editorial and scientific advisory boards for governments and industry. L. J. Wei has extensive working experience in regulatory science for developing and evaluating new drugs/devices.

Jeffrey Wilson (Ph. D. in Statistics from Iowa State University) is a Professor of Statistics and Biostatistics at Arizona State University. Dr. Wilson's research experience includes grants as PI and co-PI from the NIH, NSF, USDA, Arizona Department of Health Services, and the Arizona Disease Research Commission. He is presently the Statistics Associate Editor for The Journal of Minimally Invasive Gynecology and a former Chair of the Editorial Board of the American Journal of Public Health. He has published more than 85 articles in leading journals such as Statistics in Medicine, American Journal of Public Health, Journal of Royal Statistics Society, Computational Statistics, and Australian Journal of Statistics, among others. He has consulted with pharmaceutical companies and hospitals while representing them before the FDA and other federal government healthcare agencies. He has taught specialized Biostatistics classes at Mayo Clinic. He has led similar courses for Phoenix Children's Hospital, Barrow Neurological Center, St. Joseph's Hospital, and Banner Hospital.

Dong Xi (Ph.D. in Statistics from Northwestern University) is Associate Director in Advanced Methodology and Data Science group at Novartis. He has supported development and implementation of innovative statistical methodologies in multiple comparisons, dose finding, group sequential designs, estimands and causal inference. He has co-authored four book chapters on multiplicity and many publications in peer-reviewed journals. He is an associate editor of Statistics in Biopharmaceutical Research and Contemporary Clinical trials, and he is a committee member of the International Conference of Multiple Comparison Procedures. His work won the biennial (2019-2020) "Best Paper Award" for manuscripts published in Statistics in Biopharmaceutical Research.

Nan Xiao (Ph.D. in Statistics from Central South University, China) is an Associate Principal Scientist in Methodology Research at Merck Research Laboratories. His research interests include sparse linear models, representation learning, and computational reproducibility. He received the John M. Chambers Statistical Software Award from the American Statistical Association in 2018. His current focus is on innovative design and analysis for clinical studies through statistical methods development and robust software implementation.

Ting Ye (Ph. D. in Biostatistics from University of Wisconsin – Madison) is an Assistant Professor in the Department of Biostatistics at the University of Washington. Her research centers around addressing modern complications in randomized clinical trials and hidden biases in causal inference. In randomized clinical trials, she has developed pragmatic and robust statistical methods for delayed treatment effect in cancer immunotherapy trials, survival-time-dependent missing covariates, monotone order constraints in stratified phase II cancer trials, and covariate adjustment under covariate-adaptive randomization. In causal inference, she has expertise in instrumental variables, difference-in-differences, sensitivity analysis, and data integration.

Yilong Zhang (Ph.D. in Biostatistics from New York University) is a statistician from Merck. He is working with a group of statisticians and programmers to demonstrate the capability of using R for regulatory work. Other research interests include statistical methods in study design, missing data, and survival analysis.

DEMING CONFERENCE COMITTEE

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Monday December 6, 2021 12:00 PM – 3:00 PM

Session A
Semiparametric Regression Analysis of Interval-Censored Data

Danyu Lin, UNC-Chapel Hill
Moderator: Wenjin Wang

Interval censoring arises frequently in clinical, epidemiological, financial, and sociological studies, where the event or failure of interest is not observed at an exact time point but is rather known to occur within a time interval induced by periodic monitoring. We formulate the effects of potentially time-dependent covariates on the interval-censored failure time through semiparametric regression models, such as the Cox proportional hazards model. We study nonparametric maximum likelihood estimation with an arbitrary number of monitoring times for each study subject. We develop an EM algorithm that involves very simple calculations and converges stably for any dataset, even in the presence of time-dependent covariates. We show that the estimators for the regression parameters are consistent, asymptotically normal, and asymptotically efficient with an easily estimated covariance matrix. In addition, we extend the EM algorithm and asymptotic theory to competing risks and multivariate failure time data. Finally, we demonstrate the desirable performance of the proposed numerical and inferential procedures through simulation studies and applications to real medical studies.

Session B
Precision Gains in Randomized Studies Using Covariate Adjustment With Ordinal and Time-To-Event Endpoints

Iván Díaz, Cornell University
Moderator: Kalyan Ghosh

In this tutorial we will present new software and estimation methods for ordinal and time-to-event outcomes in randomized trials that do not rely on proportional odds/hazard assumptions. The proposed estimators leverage prognostic baseline variables to obtain equal or better asymptotic precision compared to traditional estimators. The proposed estimators have the following features: (i) they are interpretable under violations of the proportional odds/hazards assumption; (ii) they are consistent and at least as precise as the unadjusted estimators; (iii) for time-to-event outcomes, they remain consistent under violations of independent censoring (unlike the Kaplan–Meier estimator) when either the censoring or survival distributions, conditional on covariates, are estimated consistently; and (iv) they achieve the nonparametric efficiency bound when both of these distributions are consistently estimated. We will illustrate the performance of our methods using simulations based on resampling data from various completed clinical trials and from hospitalized COVID patient data. We will show that the methods achieve substantial precision gains from using covariate adjustment--equivalent to 9-21% reductions in the required sample size to achieve a desired power--for a variety of estimands (targets of inference) when the trial sample size was at least 200. We will further illustrate the use of the methods in practice using our novel R packages.

Monday December 6, 2021 3:30 PM - 6:30 PM

Session C
Group Sequential Design Under Non-Proportional Hazards
Keaven Anderson, Yilong Zhang, and Nan Xiao, Merck and Co., Inc., North Wales, PA.

Moderator: Bill Wang

We consider group sequential design for time-to-event endpoints under both proportional and non-proportional hazards assumptions for randomized clinical trials. While the primary focus will be on logrank testing due to its regulatory acceptance, weighted logrank test, combination tests and RMST will also be considered. Timing of analyses and boundary setting for efficacy and futility are critical topics to be discussed at length. A simple, piecewise model that can be used to approximate arbitrary scenarios is proposed. In addition to 2-arm comparisons for a single endpoint, we will also discuss graphical methods for strong control of Type I error when there are hypotheses for multiple endpoints and/or multiple populations. Asymptotic theory will be briefly noted as background, but the focus will be on applications, including software to quickly compare designs and scenarios. Throughout the course, we will develop designs incorporating each key new concept.

Session D
Marginal Models in Analysis of Correlated Binary Data with Time-Dependent Covariates in Biomedical Clinical Trials
Jeffrey R. Wilson and Ding-Geng Chen, Arizona State University

Moderator: Walter R. Young

This tutorial is based on the textbook: "Marginal Models in Analysis of Correlated Binary Data with Time-Dependent Covariates" co-authored by Jeffrey R. Wilson, Elsa Vazquez-Arreola, and (Din) Ding-Geng Chen, published by Springer in 2020, which uses R and SAS to conduct the computations. It provides a thorough presentation of correlated binary data with time-dependent covariates. It gives a detailed step-by-step illustration of their implementation using R and SAS.

Longitudinal data contain correlated data due to the repeated measurements on the same subject. The changing values usually consist of time-dependent covariates and their association with the outcomes present different sources of correlation. Most methods used to analyze longitudinal data average the effects of time-dependent covariates on outcomes over time and provide a single regression coefficient per time-dependent covariate. Such approaches deny researchers the opportunity to follow the changing impact of time-dependent covariates on the outcomes. This tutorial addresses such issues through the use of partitioned regression coefficients. Examples of correlated data with time-dependent covariate include *Cervical Dystonia Dataset* where data are from a multicenter, randomized controlled trial of botulinum toxin type B (BotB) in patients with cervical dystonia from nine U.S. sites measured at baseline (week 0) and weeks 2, 4, 8, 12, 16 after treatment began and *Midlife in the U.S. (MIDUS)*, a survey of adults age 25-74 in 1994/95, with ongoing longitudinal follow-up since 2002. Data includes psychosocial, behavioral, sociodemographic, and health status characteristics, and other detailed data collection for subsamples including cognitive assessments, neuroscience data, and biomarkers.

Topics to be Covered:

1. Fundamentals of estimation of regression coefficients in cross-sectional data:
    a. Ordinary least squares to obtain the regression coefficient estimates
    b. Generalized Method of Moments estimates
2. Presenting data matrix for data with time-dependent covariates. Present the partitioned matrix.
3. Present correlated data with time-dependent covariates: Illustrate longitudinal data and the analysis using linear mixed models for continuous endpoints, generalized linear mixed model, and GEE for categorical endpoints.
4. Bayesian analysis in this partitioned data matrix using MCMC is applied.

Tuesday December 7, 2021 12:00 PM – 3:00 PM

Session E

Toward Better Practice of Covariate Adjustment in Analyzing Randomized Clinical Trials

Shao Jun, University of Wisconsin – Madison and Ting Ye, University of Washington

Moderator: Naitee Ting

In randomized clinical trials, adjustments for baseline covariates at both design and analysis stages are highly encouraged by regulatory agencies. To gain credibility and efficiency, a recent trend in clinical trials is to apply covariate-adaptive randomization at the design stage and to use a model-assisted approach in analysis that further adjusts for covariate not used in design and produces asymptotically valid inference even when the model is incorrectly specified.

In this tutorial we present concepts and methodologies that are crucial for model-assisted inference based on clinical data. In particular, we introduce and elaborate three principles:
(1) guaranteed efficiency gain principle: a model-assisted method should often gain but never hurt efficiency compared with a benchmark method not utilizing covariates.
(2) validity and universality principle: a valid procedure should be universally applicable to
all commonly used randomization schemes, simple or covariate adaptive.
(3) robust standard error principle: variance estimation should be heteroscedasticity robust.

To fulfill these principles, we recommend a working model that includes all covariates utilized in randomization and all treatment-by-covariate interaction terms. Our conclusions are based on a general asymptotic theory that does not assume a correct model, is valid for most commonly used covariate-adaptive randomization schemes such as permuted block randomization and minimization, and reveals distinct results between cases of two-arm and multiple-arm trials. Numerical examples with data close to real trials are presented and discussed for illustration.

Session F

C'mon in … The DOOR is Open: Pragmatic Benefit:Risk Evaluation Using Outcomes to Analyze Patients Rather than Patients to Analyze Outcomes

Scott Evans and Toshimitsu Hamasaki, George Washington *University*

Moderator: Bill Wang

Randomized clinical trials are the gold standard for evaluating the benefits and harms of interventions. However, they often fail to provide the necessary evidence to inform medical decision-making. The important implications of these deficiencies are largely absent from discourse in medical research and biostatistical communities.

Typical analyses of clinical trials involve intervention comparisons for each efficacy and safety outcome. Outcome-specific effects are estimated and marginal effects are potentially combined in benefit:risk analyses. It is widely believed that such analyses provide comprehensive information regarding the intervention effects on patients. However such approaches do not incorporate associations between outcomes of interest, suffer from competing risk challenges when interpreting outcome-specific results, do not recognize the cumulative nature of multiple outcomes on individual patients, and since efficacy and safety analyses are often conducted using different analysis populations, the population to which such benefit:risk analyses apply, is unclear.

This deficit will be remedied in future clinical trials using thoughtful approaches with pragmatic foci. The desirability of outcome ranking (DOOR) and partial credit methodologies offer more informed patient-centric evaluation of intervention effects, providing greater utility for informing clinical decision-making. Critical components of this vision include: (i) revising the typical data analysis arithmetic to use outcomes to analyze patients rather than patients to analyze outcomes, (ii) sensitivity and robustness analyses to patient values, and (iii) identifying and evaluating subgroups based on patient-centric benefit:risk. Crucial to this approach entails improved understanding of how to analyze one patient before analyzing many. We discuss issues on the design, conduct, analyses, and reporting of clinical trials using these methods including sample size considerations, missing data and censoring considerations, and estimating subgroup effects.

Tuesday December 7, 2021 3:30 PM - 6:30 PM

Session G

Beyond Bonferroni Correction – Innovation, Intuition and Common Sense

Qian Helen Li, BMS

Moderator: Naitee Ting

In drug development and evaluation, the need for multiplicity adjustment exists in almost all phase III studies. Despite the abundant choices of statistical methods, questions remain. For example, when only one dose is included in a Phase III study, a positive study can be claimed if the 1-side p-value of the primary endpoint is 0.021. However, when two doses are included in a study and the multiplicity adjustment procedure is applied, a result such that the 1-sided p-value of the low dose is 0.021 and that of the high dose is 0.026 may not be considered as a positive study. The counter-intuitive conclusions lead to a gap in common sense, but nonetheless open opportunities for innovation. An innovated statistical method for multiplicity adjustment that can be used to address such questions will be introduced and discussed. Centered on the new method, the concept of consistent and collective evidence is introduced. Cases of application in clinical trials will be illustrated. In particular, a case of successful labeling an indication using a secondary endpoint which is in the hierarchy that the primary endpoint was failed.

Session H

Extracting Real-World Evidence from Real-World Data

Rebecca Hubbard, University of Pennsylvania and Xu Shi, University of Michigan

Moderator: Kalyan Ghosh

Interest in using real-world data (RWD), data generated outside of clinical trials, often as a by-product of digital transactions, has grown tremendously over the past decade and was further spurred by the passage of the 21st Century Cures Act. Two common sources of RWD, electronic health records (EHR) and medical claims, constitute a vast resource for the study of health conditions, interventions, and outcomes in the general population. Using RWD for research facilitates the efficient creation of large research databases, execution of pragmatic clinical trials, and study of rare diseases. Despite these advantages, there are many challenges for research conducted using RWD. To translate RWD into valid real-world evidence, statisticians must be aware of data generation, capture, and availability issues and utilize appropriate study designs and statistical analysis methods to account for these issues. This tutorial will introduce participants to the basic structure of EHR and claims data and discuss analytic approaches to working with these data through a combination of lecture and hands-on exercises in R. The first part of the course will cover issues related to the structure and quality of EHR and claims data, including data types and methods for extracting variables of interest; sources of missing data; error in covariates and outcomes extracted from RWD; and data capture considerations such as informative visit processes and medical records coding procedures. In the second half of the course, we will discuss statistical methods to mitigate some of the data quality issues arising in RWD, including missing data and error in covariates and outcomes. R code will be provided for implementation of the presented methods, and hands-on exercises will be used to compare results of alternative approaches.

Wednesday December 8, 2021 12:00 PM – 3:00 PM

Session I
The Treatment of Missing Data in Clinical Trials

Rod Little, University of Michigan
Moderator: Alfred H. Balch

This short course will discuss methods for the statistical analysis of data sets with missing values, focusing particularly on clinical trial data. Topics will include: Definition of missing data; assumptions about mechanisms, including missing at random; pros and cons of simple methods such as complete-case analysis, naïve imputation etc; Weighting methods; multiple imputation and maximum likelihood with missing data; software for handling missing data; missing data in clinical trials, focusing on the National Research Council Study findings and sensitivity analysis for deviations from missing at random.

Prerequisites: Course requires knowledge of standard statistical models such as the multivariate normal, multiple linear regression, contingency tables, as well as matrix algebra, calculus, and basic maximum likelihood for common distributions.

Outline
Module 1: Introduction and Overview
Module 2: Complete-case analysis, including weighting methods.
Module 3: Maximum Likelihood and Bayesian approaches
Module 4: Imputation, including multiple imputation
Module 5: Missing data in clinical trials

Session J
Robust Methods for Assessment of Average and Scaled Average Bioequivalence

Divan Burger, University of Pretoria, South Africa
Moderator: Din Chen

The tutorial presents robust methods for the assessment of both average and scaled average bioequivalence, based on data from conventional cross-over studies and replicate design cross-over studies. Initially, in an empirical study of a large number of average bioequivalence studies, the results of the classic and robust Bayesian analyses are compared, and the need for robust analyses is discussed. Thereafter, the classic and Bayesian robust methods are applied to a group of replicate design bioequivalence studies, and diagnostic plots and outlier diagnostics for such studies are presented. Robust analysis of replicate design bioequivalence data affects not only the estimation of the location parameters of the test and reference formulations but also the within-reference scaling factor; a proposal is made for the appropriate handling of this matter. The proposed Bayesian robust methodology is flexible with regard to study design (conventional cross-over, replicate design cross-over, parallel design) and with regard to the handling of outliers and skewness in the data.

Wednesday December 8, 2021 3:30 PM - 6:30 PM

Session K 🕮
Using SAS PROC BGLIMM and MCMC for Bayesian Analysis of Mixed Models

Walter Stroup, University of Nebraska- Lincoln

Moderator: Alfred H. Balch

Recent advances in statistical methodology and software capability have made Bayesian analysis of statistical models more accessible to data analysts. As a result, Bayesian methods have become more important. Many academic journals now discourage significance testing in favor of Bayesian inference. More importantly, the ability to use what we know prior to, or in the early stages of an investigation allow us to improve the accuracy and efficiency of statistical analysis. This tutorial introduces the SAS® system BGLIMM and MCMC procedures for Bayesian analysis. PROC BGLIMM uses syntax similar to PROC GLIMMIX to implement linear mixed models (LMMs) and generalized linear mixed models (GLMMs). PROC MCMC uses syntax similar to PROC NLMIXED and can implement non-linear, zero-inflated and semi-parametric mixed models in addition to LMMs and GLMMs. This tutorial uses examples from *SAS for Mixed Models: Introduction and Basic Applications* (Stroup, et al., 2018) and examples to appear in *SAS for Mixed Models: Advanced Applications* to introduce these two procedures and show participants what they need to know to get started with the SAS system for Bayesian analysis.

Session L
Statistical Analyses Targeting Estimands

Frank Bretz and Dong Xi, Novartis

Moderator: Ivan S F Chan

Defining the scientific questions of interest in a clinical trial is crucial to align its design, conduct, analysis, and interpretation. With the recent release of the ICH E9(R1) guideline, regulatory agencies require statistical analyses to be aligned with the target estimand(s) which precisely describe the treatment effect(s) of interest that a clinical trial should address. For a given estimand, an aligned method of analysis, or estimator, should be implemented that is able to provide an estimate on which reliable interpretation can be based and which includes the handling of post-randomization events, missing data and sensitivity analyses. Many statistical analysis procedures are available for different types of data, although it is often unclear which estimands these imply. In this tutorial, we discuss how to identify and implement analyses approaches as well as sensitivity analyses that are aligned with a chosen estimand for different types of endpoints (continuous, binary, time-to-event, recurrent events) in longitudinal clinical trial settings. We illustrate the methods with real case studies and provide code examples to facilitate implementation in practice.

SHORT COURSE

Registration includes electronic handouts. The book used in the short course is not included in the registration fee. Registrants are responsible to purchase the book themselves. The conference offers a discounted price on book sales. No registrations will be accepted without payment in full. We will refund full tuition if courses are canceled due to insufficient registration.

Daily Schedule: 11:00 AM⇒12:30 PM Lecture/ 12:30 PM ⇒ 1:00 PM *Break*/ 1:00 PM⇒2:30 PM Lecture / 2:30 PM⇒ 2:50 PM *Break* / 2:50 PM⇒4:20 PM Lecture / 4:20 PM⇒4:30 PM *Break* / 4:30 PM ⇒ 6:00 PM Lecture

December 9-10, 2021

Estimands, Missing Data Handling, and Bayesian Methods for Clinical Trials

Frank Liu, Merck & Co. Inc and Fang Chen, SAS® Institute Inc.

Moderator: Ivan S. F. Chan

Missing data often occur in longitudinal and survival clinical trials due to early discontinuation. The problem is closely associated with the estimand framework and assumptions about missing data and censoring. How to handle the missing data is critical in analysis of clinical trials. Methods such as likelihood-based approaches, multiple imputation, and Bayesian approaches are often considered.

The course will provide overview of estimand frameworks, missing data methods for longitudinal and survival trials, and Bayesian approaches for handling missing data as well as for borrowing historical data, and illustrate how to implement these analyses methods using SAS.

Course outlines:

Day 1

- Review of estimands, concept of intercurrent events vs missing data
- Missing data methods for longitudinal trials
  - maximum likelihood methods: MMRM, cLDA
  - multiple imputation
  - generalized estimation equation approaches: GEE, wGEE
  - Repeated binary endpoints
- Introduction of Bayesian Method
  - Bayesian software
  - PROC MCMC
  - PROC BGLIMM
  - Examples
- Sensitivity analysis methods
  - General methods for missing not at random
  - More recent approaches
    - Control-based imputation
    - Control-based mean imputation
    - Baseline-based imputation

Day 2

- Sensitivity analysis methods (cont.)
  - More recent approaches
    - Delta-adjustment methods and tipping point analysis
    - Dropout as poor outcome
  - Bayesian sensitivity analysis
- Missing data methods for survival trials
  - Censoring issue in survival trials
  - Sensitivity analysis methods
    - Control-based imputation
    - Delta-adjustment methods
    - Tipping point analysis
  - Bayesian sensitivity analysis
- Information borrowing with Bayesian
  - Incorporation of Historical Data
    - Power prior
    - Hierarchical Models
    - Commensurate priors
    - Meta analytic predictive prior
  - Prior distributions in hierarchical models

Dr. **Frank Liu** is a distinguished scientist at Merck & Co., Inc. and a Fellow of the American Statistical Association. For more than 26 years at Merck, Frank has worked on various therapeutical areas and conducted research in longitudinal trials, missing data, noninferiority trials, and Bayesian methods; and served as a technical consultation and leading the development of many methodological guidance documents. Before joining Merck, he received his PhD in statistics from UCLA and completed a post-doc in Biostatistics at Johns Hopkins University.

Dr. **Fang Chen** is Direcor of Analytical Software Development at SAS Institute Inc. and a Fellow of the American Statistical Association. He manages the development of statistical software for SAS/STAT®, SAS/QC®, and analytical components that drive SAS® Visual Statistics software. Also among his responsibilities is the development of Bayesian analysis software and the MCMC procedure. Before joining SAS, he received his PhD in statistics from Carnegie Mellon University.

THREE KEYNOTES

(Monday, Tuesday, and Wednesday Morning, December 6-8, 2021, 11 AM - 12:00 PM)

Keynote 1: What is Translational Biostatistics and How to Implement It?

L. J. Wei, Harvard University
Moderator: Pinggao Zhang

Over the years, the process of designing, monitoring, and analyzing clinical studies for evaluating new treatments has gradually fallen into a fixed pattern. Clinical trialists have sometimes been slow to utilize new methodologies–perhaps to avoid potential delays in the review process for treatment approval or manuscript submission. The underlying attitude toward innovation in drug development is in sharp contrast to that in other technologically-driven fields. Scientific investigation is an evolving process. What we have learned from previous studies about methodological shortcomings should help us better plan and analyze future trials. Unfortunately, use of inefficient or inappropriate procedures persists even when better alternatives are available. In this talk, we will explore various methodological issues and potential solutions to them. A goal of the clinical study is to obtain robust, clinically interpretable treatment effect estimate with respect to risk-benefit perspectives at the patient's level via efficient and reliable quantitative procedures. We will discuss how to achieve this goal via various real trial examples.

Keynote 2: Current Trends in Multiple Imputation

Stef van Buuren, University of Utrecht, Holland
Moderator: Alfred H. Balch

Multiple imputation is a principled approach to deal with missing data. In this lecture, we discuss the evolution of the technology since the 70's until now, and identify new problems that surface in the context of big data, machine learning, flowing data, network problems and other problems of current interest.

Keynote 3: Two Key Ideas in Missing Data – Missing at Random and Response Propensity

Rod Little, University of Michigan
Moderator Alfred H. Balch

I discuss the definition of two key concepts in the analysis of data with missing values, missing at random (MAR) and response propensity. Don Rubin defined MAR as a sufficient condition for ignoring the missingness mechanism for likelihood-based and Bayesian inference. Some simple examples of MAR are described, and related concepts, including missing completely at random, always missing at random, always missing completely at random, partially missing at random, informative missingness, informative censoring, and coarsening at random are discussed. I present a formal argument for weakening Rubin's sufficient conditions for frequentist maximum likelihood inference with precision based on the observed information. The definition of response propensity is often misunderstood, particularly in the survey sampling literature, because of ambiguity about conditioning. A definition that resolves this ambiguity is suggested, by clarifying that dependence on unobserved variables is superfluous for the purpose of nonresponse adjustments.

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