NIC-ASA

ICSA Midwest

NIC-ASA and ICSA Midwest Chapter Joint Fall Meeting

October 24-25, 2019

Hilton Chicago/ Northbrook
Northbrook, IL 60062

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Short Courses

October 24, 2019

9:00am - 12:00pm (XXX)

Title: Causal inference in real world observational data

Instructor: *Douglas Faries and Xiang Zhang, Eli Lilly*

Abstract:

Bio: Dr. Douglas Faries

Bio: Dr. Xiang Zhang

October 24, 2019 **1:30pm - 4:30pm** (XXX)

Title: Learning and Implementing Bayesian Adaptive Designs

Abstract: Clinical trial is a prescribed learning process for identifying safe and effective treatments. In recent years, rapid advancements in cancer biology, immunology, genomics, and novel treatments demand innovative methods to better identify effective therapies for the most appropriate population in a timely, efficient, accurate, and cost-effective way. In this short course, I will first illustrate the concept of Bayesian update and Bayesian inference, a superior alternative to the traditional frequentist approach. Bayesian methods take the "learn as we go" approach and are innately suitable for clinical trials. Then, I will give an overview of Bayesian adaptive designs in the areas of adaptive dose finding, posterior probability and predictive probability calculation, outcome adaptive randomization, multi-endpoint phase II design, multi-arm platform design, and hierarchical modeling, etc. Particular attention will be devoted on the model assisted designs including the BOIN design and the BOP2 design for Phase I and Phase II trials, respectively. Shiny applications for the design and conduct of clinical trials will be introduced. (http://trialdesign.org).

Bayesian adaptive clinical trial designs increase the study efficiency, allow more flexible trial conduct, and treat more patients with more effective treatments in the trial but also possess desirable frequentist properties. Perspectives will be given on the future development in clinical trial design, conduct, and evaluation with the goal to enhance success and speed up the drug approval process.

Instructor: J. Jack Lee, PhD, DDS
Professor & Associate Vice President – Quantitative Sciences
Department of Biostatistics
The University of Texas MD Anderson Cancer Center

Dr. Lee's areas of research interest include design and analysis of clinical trials, survival analysis, longitudinal data

analysis, statistical computation/graphics, statistical methods for determining drug interaction in combination studies, and cancer chemoprevention. Dr. Lee has been working on the development and application of innovative Bayesian methods for cancer clinical trials. He also actively participates in many multidisciplinary translational research. He has particular interests in incorporating multiple biomarkers and adaptive designs to develop more efficient and ethical clinical trials. Dr. Lee is a Statistical Editor for the *Journal of the National Cancer Institute* and *Cancer Prevention Research*. He is a Fellow of the American Statistical Association and Society for Clinical Trials.

Reception

October 24, 2019

4:30pm – 6:30pm (Franks Place)

Free for all registers.

Free on the spot photo magnets (2hrs $600)!

Main Program

October 25, 2019

8:00 – 9:00 am	Registration **(Garden Terrance)** and Breakfast **(Willow & Pine)**
9:00 – 9:15 am	**Opening Remarks (Willow & Pine)** *Lanju Zhang (AbbVie Inc.) & Li Wang (AbbVie Inc.Inc.)*
9:15 –10:00 am	**Keynote Address (Willow & Pine)** **How to stand out from the crowd – Secrets to career success in Statistics** *Erik Pulkstenis, VP DSS(AbbVie Inc.)*
10:00 –10:15am	Break/Networking
10:15–11:15 am	Parallel Session 1: Evaluating performance of covariate-constrained randomization techniques **(Pine)**
	Parallel Session 2: Survival Analysis beyond Proportional Hazard Model **(Willow)**
10:15–11:15 am	Parallel Session 3: Multiplicity Issues in Clinical Trials **(Pine)**
	Parallel Session 4: Statistical Modeling in Phase II Dose Finding Studies **(Willow)**
12:05–1:30 pm	Lunch **(Pondview & Upper Sect)**
8:00–4:00 pm	Student Poster Exhibition **(Linden I & II)**
12:35 – 1:30 pm	Student Poster Q&A Session **(Linden I & II)**
1:30 – 2:50 pm	Parallel Session 5: Deep Learning Methods for Big Data **(Pine)**
	Parallel Session 6: Use of Real World Evidence for Regulatory Decisions **(Willow)**
2:50 – 3:00 pm	Break/Networking
3:00 – 4:00 pm	Parallel Session 5 Statistical Considerations

	in Late Phase Clinical Trials **(Pine)**
	Parallel Session 6: Advanced Statistical Methods in Clinical Trial Design **(Willow)**
4:00 – 4:30 pm	Student Awards and Closing Remarks **(Willow & Pine)** *Lihui Zhao (Northwestern University)* *Li Wang (AbbVie Inc.)*

Keynote Address

Title: How to stand out from the crowd – Secrets to career success in Statistics

Abstract: optional

Speaker: *Erik Pulkstenis, PhD*

VP Data and Statistical Sciences (AbbVie Inc.)

Erik Pulkstenis joined AbbVie in 2018 as the Vice President and Global Head of Data and Statistical Sciences in support of clinical development strategy, data collection, statistical analysis and reporting. Dr. Pulkstenis brings to AbbVie more than 20 years of experience in drug and device development and clinical research. He has demonstrated success building, rehabilitating and leading biostatistics and data management departments and he is passionate about leadership and culture. He also has more than 25 peer-reviewed publications including one textbook and has directly supported 11 FDA approvals. Previously, Dr. Pulkstenis headed Clinical Biostatistics & Data Management at Medimmune, where he established the organizational infrastructure, underlying operating model and all associated processes in support of a diverse pipeline focused on immunology, immuno-oncology, and cardiovascular disease. Prior to that, Dr. Pulkstenis led the Biostatistics Department at Human Genome Sciences, and served at C.L. McIntosh & Associates consulting with medical device manufacturers with respect to study design, regulatory strategy, and FDA Advisory Committee preparation. Dr. Pulkstenis currently serves on the American Statistical Association Biopharmaceutical Section Executive Committee. Dr. Pulkstenis received an M.S. and Ph.D. in statistics from the Pennsylvania State University.

Parallel Sessions

10:15 am – 11:15 am

Session 1: **Evaluating performance of covariate constrained randomization techniques (Pine)** *Organizer: Julie Lee (Northwestern University)* *Chair: Julie Lee (Northwestern University)*	
10:15– 10:35	**Handling Covariates in Randomized Controlled Trials, Medicine** *Jody Ciolino (Northwestern University Feinberg School of Medicine)*
10:35 – 10:55	**Quantile Lost Lifespan in Clinical Trials** *Lauren Balmert (Northwestern University Feinberg School of Medicine)*
10:55 – 11:15	**Design Considerations for Cluster-Randomized Trials** *Madeleine Organ (Press Ganey)*

Session 2: **Survival Analysis beyond Proportiona Hazard Model (Willow)** *Organizer: XXX (Astellas Pharma Inc.)* *Chair: XXX (Astellas Pharma Inc.)*	
10:15– 10:35	**Weighted Log-rank Test for Time-to-event Data in Immunotherapy Trials with Random Delayed Treatment Effect and Cure Rate** *Shufang Liu* (Astellas); Alan Rong(Astellas); Chenghao Chu (Vertex)*
10:35 – 10:55	**Implementation of weighted log-rank test in clinical trial with interim look to preserve overall type-I error** *Madan Kundu (AbbVie)*
10:55 – 11:15	**Application of modulated Markov models and modulated renewal process for analyzing clinical trial data with non-proportional hazards** *Rianka Bhattacharya (AbbVie)*

11:25 pm – 12:05 pm

Session 3: **Multiplicity Issues in Clinical Trials** (Pine) *Organizer: XXX (AbbVie Inc.)* *Chair: XXX (AbbVie Inc.)*	
11:25 – 11:45	**Utilization a group-sequential graphical approach for multiplicity control in registration clinical trials with multiple doses, multiple endpoints and interim analyses** *Deli Wang (AbbVie)*
11:45 – 12:05	**SAS implementation of the graphical multiple testing procedure for single and families of hypotheses** *Xianwei Bu (Abbvie)*

Session 4: **Statistical Modeling in Phase II Dos Finding Studies (Willow)** *Organizer: Annie Wang (Astellas Pharma Inc.)* *Chair: Misun Lee (Astellas Pharma Inc.)*	
11:25 – 11:45	**Joint Modeling for Co-Primary Continuous Endpoints in Phase II Dose Finding** *Qi Yan (Astellas Pharma Inc.)*
11:45 – 12:05	**Joint MCP-Mod for Two Sets of Dosing Regimens in Phase II Dose Finding** *Annie Wang (Astellas Pharma Inc.)*

1:30 pm – 2:50pm

Session 5: **Deep Learning Methods for Big Data (Pine)** *Organizer: Lihui Zhao (Northwestern University)* *Chair: Lihui Zhao (Northwestern University*	
1:30 –	**Mapping robust trans-associations via cross-condition mediation analyses and validating trait-associations**

1:50	**of trans-genes for GWAS SNPs** *Lin Chen (University of Chicago)*
1:50 – 2:10	**MUCE: A Bayesian Design for Phase 1b Multiple Expansion Cohort Trials** *Yuan Ji(University of Chicago)*
2:10 – 2:30	**Neural Network Approaches to Predicting Enhancer-Promoter Interactions with DNA Sequence Data and/or Epi-genomic Data** *Wei Pan (University of Minnesota)*
2:30 – 2:50	**Differential footprint analysis in Ribo-seq data** *Jiping Wang (Northwestern University)*

Session 6: **Use of Real World Evidence for Regulatory Decisions (Willow)** *Organizer: Xiang Zhang (Eli Lily and Company)* *Chair: Doug (Eli Lily and Company)*	
1:30 – 1:50	**Building and Validating Real-World Control Arms for Clinical Trials: Challenges and Best Practices** *Zhanglin Cui (Eli Lilly)*
1:50 – 2:10	**A Case Study for Achieving Regulatory Approval using Match Analysis with Registry Database,** *Misun Lee (Astellas)*
2:10 – 2:30	**A statistical roadmap for journey from real-world data to real-world evidence** *Yixin Fang (AbbVie)*
2:30 – 2:50	**Meeting RWE Evidentiary Standards in a Changing World** *Yonghua Jing (AbbVie); David Van Brunt (AbbVie)*

3:00 pm – 4:00 pm

Session 7: **Statistical Considerations in Late Phas Clinical Trials (Pine)** *Organizer: XXX (Northwestern University)* *Chair: XXX (Northwestern University)*	
3:00– 3:20	**Causal inference and estimands in clinical trials** *Ilya Lipkovich (Eli Lilly)*
3:20 – 3:40	**A quantitative benefit-risk assessment method for medical product decision-making** *Bo Fu (Astellas)*
3:40 – 4:00	**Evaluation of statistical methods for longitudinal data analysis with dropout under MNAR assumption** *Yiran(Bonnie) Hu (AbbVie)*

Session 8: **Advanced Statistical Methods in Clinica Trial Design(Willow)** *Organizer: XXX (Astellas Pharma Inc.)* *Chair: XXX (Astellas Pharma Inc.)*	
3:00– 3:20	**Longitudinal dose response surface model and its application in trial decision making** *Ran Duan (Eli Lilly)*
3:20 – 3:40	**2-in-1 adaptive design and evaluation for delayed response** *Chaofeng Liu (Astellas)*
3:40 – 4:00	**Modified Goldilocks Design with Strict Type I Error Control in Confirmatory Clinical Trials** *Tianyu Zhan (AbbVie)*

Abstracts

Session 1: **Novel Statistical Methods for High Dimensional and Complex Data (Salon C)**

Organizer: Lihui Zhao (Northwestern University)
Chair: Lihui Zhao (Northwestern University)

10:20 – 10:40	**Simultaneous estimation and inference for high-dimensional linear models** *Yi Li (University of Michigan)* **Abstract:** Drawing inferences for high-dimensional models is challenging as regular asymptotic theories are not applicable. This talk proposes a new framework of simultaneous estimation and inference for high-dimensional linear models. By smoothing over partial regression estimates based on a given variable selection scheme, we reduce the problem to a low-dimensional least squares estimation. The procedure, termed as Selection-assisted Partial Regression and Smoothing (SPARES), utilizes data splitting along with variable selection and partial regression. We show that the SPARES estimator is asymptotically unbiased and normal, and derive its variance via a nonparametric delta method. The utility of the procedure is evaluated under various simulation scenarios and via comparisons with the de-biased LASSO estimators, a major competitor. We apply the method to analyze two genomic datasets and obtain biologically meaningful results.

10:40 – 11:00	**Semi-Parametric Inference with Non-Stationary Non-Gaussian Temporally Dependent Errors** *Chunming Zhang (University of Wisconsin-Madison)* **Abstract:** Motivated from the brain fMRI data analysis, this talk presents a new semi-parametric inference procedure applicable to a broad class of "non-stationary non-Gaussian temporally dependent" error processes for time-course data collected at spatial points. A new test statistic will be developed based on an efficient estimator of the large temporal-error auto-covariance matrix, and its asymptotic distribution will be established. Applications to fMRI data will be illustrated.
11:00 – 11:20	**Score-Matching Representative Approach for Big Data Analysis with Generalized Linear Models** *Jie Yang (University of Illinois at Chicago)* **Abstract:** We propose a fast and efficient strategy, called the representative approach, for big data analysis with linear models and generalized linear models. With a given partition of big dataset, this approach builds up a representative data point for each data block and fit the target model on the representative dataset. In terms of time complexity, it is as fast as the subsampling approaches in the literature. As for efficiency, its accuracy of the estimated parameters is comparable or better than the divide-and-conquer method. More specifically, we recommend two representative approaches, mean representative (MR) and score-matching representative (SMR), along with theoretical justifications, for big data analysis with generalized linear models. Comprehensive simulation studies confirm that MR and SMR outperform the subsampling and divide-and-conquer methods in the

	literature, and SMR estimate is even comparable with the full data estimate with properly chosen data partition. Using the Airline on-time performance data as an illustrative real data example, we show that our solutions are as good as the full data estimate when available. In addition, the representative strategy is especially useful when analyzing massive data dispersed over a network of interconnected computers.
11:20 – 11:40	**Computational methods for investigating microbial interactions** *Hongmei Jiang (Northwestern University)* **Abstract:** Numerous evidences have shown that the microbes living on and inside our body are associated with the occurrence and progression of many diseases and the response to treatment. Next generation sequencing technologies provide a powerful tool to study metagenomics. In this talk we will talk about how to characterize the microbial interactions based on 16S sequencing data. Different normalization methods for metagenomics data will also be discussed.
Session 2: **Design and Analysis in Oncology Clinical Studies (Salon D)** *Organizer: Shufang Liu (Astellas Pharma Inc.)* *Chair: Lei Shu (Astellas Pharma Inc.)*	
10:20 – 10:45	**A numerical evaluation of statistical methods on testing non-PH survival data** *Danting Zhu (University of Michigan), Tu Xu (AbbVie Inc., Jia Jia (AbbVie Inc.)* **Abstract:** In the era of immune-oncology, the non-proportional hazard (PH) pattern has been

	frequently observed in the analysis of time-to-event endpoints, such as progression-free survival (PFS) and overall survival (OS). The traditional analysis methods, such as log-rank test and Cox model, could yield suboptimal performance on power when comparing the treatment arms. In this talk, we will review the development of statistical methods on testing the time-to-event data and compare their performance via simulations the non-proportional hazard setting.
10:45 – 11:10	**A Predictive Approach and Sensitivity Analysis for Time-to-Event Data with Informative Censoring** *Wei Li (Astellas Pharm Inc.), Misun Lee (Astellas Pharm Inc.), Zhiwei Zhang (University of California at Riverside)* **Abstract:** In many clinical trials, an important outcome is treatment success, such as tumor response or disease remission. It is often of interest to analyze the time to such outcome. A time-to-event analysis of treatment success is uniquely challenging because it is prone to informative censoring. Traditional survival analysis methods, including Kaplan-Meier estimator and log-rank test, rely on the strong assumption of noninformative censoring. In time-to-success data, this assumption is often questionable. For example, subjects who died or dropped out due to worsening disease status may have been censored informatively. As a result, standard survival analysis methods often yield invalid estimates and inferences for time to success. We propose a methodology for estimation and testing that accounts for subject-specific censoring mechanisms, which may be informative. We use a censored subject's observed relevant data to determine his/her "differential parameter" value,

	which is a quantification of the subject's censoring mechanism. We incorporate a subject's specific differential parameter value to predict his/her probabilities of having the event of interest at each post dropout time point and subsequently obtain the estimate and two-sample test statistic of cumulative incidence curve. Like all methods for informative censoring, sensitivity analysis is essential. The proposed methodology allows for easy and transparent implementation of sensitivity analysis, which is used to discover the range (and robustness) of study results under various plausible assumptions about subjects' censoring mechanisms. We apply the proposed methodology to an infectious disease clinical trial and conduct a sensitivity analysis. While motivated by the time-to-success analysis, our methodology can be applied to other time-to-event data with informative censoring.
11:10 – 11:35	**Incorporating the Variability of Biomarker Prevalence into Late Phase Clinical Trial Design (IVBP)** *Hong Wang (Eli Lily Company), Dan Wang (Eli Lily Company)* **Abstract:** Incorporating biomarker information into drug development has become increasingly more important for the more precise identification of the right target population who can benefit from a specific therapy. In recent years, an increasing variety of biomarker-driven clinical trial designs have been utilized in clinical drug discovery and development, e.g. fixed-sequence design, fallback design, and treatment-by-biomarker interaction design. The prevalence of the targeted biomarker population is a critical input in these biomarker trial designs. These designs consider prevalence as a known and fixed parameter in the model. However,

	a meta-analysis using clinical trial data and real word evidence showed that the variability of the prevalence can be high due to sampling variability, assay variability, and other operational details. Here we propose a new method (IVBP) to address this issue. Our simulation results showed that IVBP improved the efficiency of the estimate compared to traditional methods as well as the precision in estimating the treatment efficacy.
Session 3: **Recent Advances in Machine Learning and Data Mining (Salon C)** *Organizer: Lei Liu (Washington University in St. Louis)* *Chair: Xin Huang (AbbVie Inc.)*	
1:30 – 1:55	**Evaluation Measures in Data Mining** *Wenxing Jiang (Northwestern University)* **Abstract:** We study some useful performance measures in data mining and derive the asymptotic distributions of their sample estimates. These allow us to construct two types of confidence intervals: one based on the plug-in estimates of the asymptotic variances, another based on re-sampling. Some numerical studies are performed to illustrate and compare these methods.
1:55 – 2:20	**A sparse clustering algorithm for identifying cluster changes across conditions with applications in single-cell RNA-sequencing data** *Jun Li (University of Notre Dame)* **Abstract:** Clustering analysis, in its traditional setting, identifies groupings of samples from a single population/condition. We consider a different setting when the data available are samples from two different conditions, such as cells before and after drug treatment. Cell types in cell populations change as the condition changes: some cell types die

	out, new cell types may emerge, and surviving cell types evolve to adapt to the new condition. Using single-cell RNA-sequencing data that measure the gene expression of cells before and after the condition change, we propose an algorithm, SparseDC, which identifies cell types, traces their changes across conditions, and identifies genes which are marker genes for these changes. By solving a unified optimization problem, SparseDC completes all three tasks simultaneously. As a general algorithm that detects shared/distinct clusters for two groups of samples, SparseDC can be applied to problems outside the field of biology.
2:20 – 2:45	**Noise Injection Regularization in Large Models with Applications to Neural Networks and Graphical Models** *Fang Liu (University of Notre Dame)* **Abstract:** The noise injection regularization technique (NIRT) is an approach to mitigate over-fitting in large models. In this talk, I will demonstrate the applications of the NIRT in two scenarios of learning large models: Neural Networks (NN) and Graphical Models (GM). For NNs, we develop a NIRT called whiteout that injects adaptive Gaussian noises during the training of NNs. We show that the optimization objective function associated with whiteout in generalized linear models has a closed-form penalty term that has connections with a wide range of regularizations and includes the bridge, lasso, ridge, and elastic net penalization as special cases; it can also be extended to offer regularizations similar to the adaptive lasso and group lasso. For GMs, we develop an AdaPtive Noisy Data Augmentation regularization (PANDA) approach to promote sparsity in estimating individual graphical models and similarity among multiple graphs

	through training of generalized linear models. On the algorithmic level, PANDA can be implemented in a straightforward manner by iteratively solving for MLEs without constrained optimizations. For both the NN and PANDA approaches, we use simulated and real-life data to demonstrate their applications and show their superiority or comparability with existing methods.
Session 4: **Real World Evidence (RWE) and Its Application in Clinical Development (Salon D)** *Organizer: Weili He (Abbvie Inc.)* *Chair: Weili He (AbbVie Inc.)*	
1:30 – 1: 55	**Regulatory Grade Real World Evidence: Filling in the Gaps** *Doug Faries (Eli Lilly and Company.)* **Abstract:** The passing of the 21st Century Cures Act and PDUFA VI has accelerated the discussion about the potential for expanded use of real world evidence (RWE) for regulatory decision-making. While there is growing debate and great promise, current examples of use of RWE for approval are limited to rare diseases as well as safety related questions. A pathway toward broader regulatory use of RWE could lead to more patient focused research that could be generalizable to a broader population group and relevant to payers, patients, and prescribers. However, key data quality, design and analytical challenges remain – such as the uncertain operating characteristics of comparative effectiveness. In this talk, we will discuss methodological issues and innovations that could improve the operating characteristics of real world research and thus move the field closer to regulatory grade RWE. Discussions will include research designs, such as the value and challenges of pragmatic trials, as well as methodological

	improvements for bias control and addressing unmeasured confounding.
1:55 – 2:20	**Robust Real-World Evidence Generation: Data Source and Analytic Framework** *Hongwei Wang (Abbvie Inc.)* **Abstract:** While well designed randomized clinical trials remain the gold standard to establish efficacy and safety profile of a medical intervention, their generalizability to a wider population and lack of head to head comparison with relevant treatment options warrants further research. Real world evidence, including comparative effectiveness research, plays a critical role in filling this gap. Large varieties of real-world data sources exist and continue to be accumulated in the current digital age. Each type is associated with its strengths and limitations which need to be factored into study design and analysis. Further, as no randomization is involved, selection bias leads to imbalance of key patients' characteristics across different comparison groups. Various analytic frameworks have been proposed to control for this inherent confounding, which include conditional model of multivariate regression and marginal model of propensity score (PS) based method. The performance of these methods in terms of bias reduction, coverage of confidence interval, power to detect a true difference, and Type I error control require evaluation. In this talk, we will go over main types of real-world data sources and present findings from a simulation study evaluating the performance characteristics of a few commonly used methods with recommendations for their practical usage.
2:20 – 2:45	**Evaluating Instrumental Variables Based on Healthcare System Characteristics in Observational Studies** *Dongmu Zhang (Abbvie Inc.)*

	Abstract: As the primary purpose of health insurance claims databases is billing, certain characteristics of patients are not recorded, making the studies using these sources vulnerable to unmeasured confounding. Using an empirical example of the association between osteoporosis medication use/no use and the risk of osteoporotic fractures, this study found that healthcare system characteristics can serve as IVs to adjust for unmeasured confounding.
Session 5: **Bayesian Design and Decision in Clinical Development (Salon C)** *Organizer: Xiang Zhang (Eli Lilly and Company)* *Chair: Tu Xu (AbbVie Inc.)*	
3:00 – 3: 25	**BOIN-ET: Bayesian optimal interval design for dose finding based on both efficacy and toxicity outcomes** *Kentaro Takeda (Astellas Pharma Inc.), Masataka Taguri (Yokohama City University, Japan), Satoshi Morita (Kyoto University, Japan)* **Abstract:** One of the main purposes of a phase I dose-finding trial in oncology is to identify an optimal dose (OD) that is both tolerable and has an indication of therapeutic benefit for subjects in subsequent phase II and III trials. Many phase I dose-finding methods based solely on toxicity considerations have been proposed under the assumption that both toxicity and efficacy monotonically increase with the dose level. Such an assumption may not be necessarily the case, however, when evaluating the OD for molecular targeted, cytostatic, and biological agents, as well as immune-oncology therapy. To address this issue, we extend the Bayesian optimal interval (BOIN) design,

	which is nonparametric and thus does not require the assumption used in model-based designs, in order to identify an OD based on both efficacy and toxicity outcomes. The new design is named "BOIN-ET." A simulation study is presented that includes a comparison of this proposed method to the model-based approaches in terms of both efficacy and toxicity responses. The simulation shows that BOIN-ET has advantages in both the percentages of correct OD selected and the average number of patients allocated to the ODs across a variety of realistic settings.
3:25 – 3:50	**Bayesian hierarchical model for meta-analysis in historical data borrowing** *Zailong Wang (AbbVie Inc.), Zhuqing Yu(AbbVie Inc.)* **Abstract***:* For binary outcomes, Bayesian hierarchical models for meta analysis in historical data borrowing will be illustrated for clinical trial design and analysis. Comparison between Beta-Binomial model and Normal-Normal model from simulation results will be discussed based on operating characteristics such as Type I error and power. Examples for historical data borrowing with Bayesian hierarchical models will be presented.
3:50 – 4:15	**The use of design priors in informing decision criteria of clinical programs – a case study** *Forest Willimson (Eli Lily and Company)* **Abstract:** Clinical trial optimization traditionally seeks to analyze data in a way which, for a pre-determined significance level, may either maximize power given a fixed sample size, or minimize sample size given a lower limit on power. Simulation allows the statistician to investigate operating characteristics of a trial under various scenarios of truth – one of which would include an 'expected' scenario on which the trial design is based. Other

	scenarios should also be investigated, including at minimum: a pessimistic effect (worse than expected), an optimistic effect (better than expected), and a null effect to evaluate Type I error. These fixed scenarios do not take in to account the relative uncertainty between scenarios, nor do they offer a way of looking at the clinical program under that uncertainty. Design priors are a way to average over the uncertainty in the drug effect, and may offer a better way to tune design specifications to provide more desirable operating characteristics than under an assumption of a fixed effect. In this talk, we will introduce the design prior and go through a case example in Alzheimer's disease.
Session 6: **Estimand and MCPMod (Salon D)** *Organizer: Zailong Wang (AbbVie Inc.)* *Chair: Julia Lee (Northwestern University)*	
3:00 – 3: 25	**The Estimand in Clinical Trial Design: Applications to Protocols, SAPs and our Clinical Colleagues** *Lois Larsen (AbbVie Inc.)* **Abstract:** At this point most statisticians understand the 4 elements of an estimand. They may even understand the 5 strategies for addressing intercurrent events, and the difference between a new estimand and a sensitivity analysis. But have we convinced clinicians of the importance of determining all 4 elements of an estimand before designing a clinical trial. Can we reach agreement on how to incorporate estimands into protocols and statistical analysis plans? After a quick review of the former, we will discuss how to get buy in for the inclusion of estimands in clinical trial design, and provide examples of inclusion of estimands in protocols and SAPs.

3:25 – 3:50	**Appropriate Estimands and Estimators** *Grace Li, Yongming Qu, Haoda Fu, Lei Shen, and Alan Chiang (Eli Lily and Company)* **Abstract:** The ICH E9 (R1) Addendum "Estimands and Sensitivity Analysis in Clinical Trials" as a draft guideline is adopted by many regulatory bodies including EMA and FDA. This document establishes a framework to align planning, design, conduct, analysis, interpretation for a registration clinical study. The choice of the estimands is determined by the study objective and the agreement within the study team, and between sponsors and regulators. Appropriate estimator along with the estimand is essential to address the specific clinical questions. This presentation will focus on the differences among different estimands and different ways to handle intercurrent events using simulation.
3:50 – 4:15	**MCP-Mod based Quantitative Techniques for Decision Making Process in Phase II Dose-finding Clinical Trials** *Annie Wang (Astellas Pharma Inc.), Na Cai (Astellas Pharma Inc.), Mike Smith (Astellas Pharma Inc.)* **Abstract:** Informed decisions on moving a drug to phase III based on phase II data mitigates late-stage failure risk. Many quantitative techniques beyond p-values incorporating additional metrics have been developed for decision making. We extend the decision making process to Multiple Comparison Procedure and Modeling (MCP-Mod) based phase II dose finding studies. MCP-Mod is an efficient statistical method for model-based design and analysis of phase II dose-finding studies, which has been endorsed by regulatory agencies. The modeling approach in MCP-Mod allows us to integrate all available data and interpolate information across

	dose levels and hence provides more information and a solid basis for decision making. We will discuss the practical issues in MCP-Mod based decision making and propose various quantitative techniques based on bootstrap model averaging method. Simulation studies were performed to evaluate the performance and robustness of the proposed techniques under different scenarios. Key words: Bootstrap, Clinical Trials, Dose-Finding, MCP-Mod, Quantitative Decision Making