**TUESDAY MORNING WORKSHOP (8:30 am – 11:30 am)**

**A. (CLINICAL) Covariate adjustment in clinical trials**

**Organizer/Chair: Andy Wey, Eli Lilly**

**1. Covariate Adjustment in Bayesian Adaptive Clinical Trials**

 **Speaker: James Willard, McGill University**

In conventional randomized controlled trials, adjustment for baseline values of covariates known to be associated with the outcome (covariate adjustment) increases the power of the trial. Recent work has shown similar results hold for more flexible frequentist designs, such as information adaptive and adaptive multi-arm designs. However, covariate adjustment has not been characterized within the more flexible Bayesian adaptive designs, despite their growing popularity. We focus on a subclass of these which allow for early stopping at an interim analysis given evidence of treatment superiority. We consider both collapsible and non-collapsible estimands, and show how to marginalize posterior samples of conditional estimands. We describe several estimands for three common outcome types (continuous, binary, time-to-event). We perform a simulation study to assess the impact of covariate adjustment using a variety of adjustment models in several different scenarios. This is followed by a real world application of the compared approaches to a COVID-19 trial with a binary endpoint. For all scenarios, it is shown that covariate adjustment increases power and the probability of stopping the trials early, and decreases the expected sample sizes as compared to unadjusted analyses.

**2. Toward Better Practice for Covariate Adjustment in Randomized Clinical Trials**

 **Speaker: Ying Zhang, Eli Lilly**

Since the FDA released a revised draft guidance for industry on Adjustment for Covariates in Randomized Clinical Trials for Drugs and Biological Products in May 2021, there has been increased interest in using covariate-adjusted analyses to improve efficiency for demonstrating and quantifying treatment effects. In this talk, we will first provide an overview of the key elements and concepts of covariate adjustment. Then we will present covariate adjustment methods for continuous, discrete, and time-to-event outcomes. An R package RobinCar (https://github.com/tye27/RobinCar) is available to implement all proposed methods.

**3. Robustly Leveraging Post-Randomization Information to Improve Precision in Randomized Trials**

 **Speaker: Yu Du, Eli Lilly**

In randomized trials, repeated measures of the outcome are routinely collected. The mixed model for repeated measures (MMRM) leverages the information from these repeated outcome measures, and is often used for the primary analysis to estimate the average treatment effect at the primary endpoint. MMRM, however, can suffer from bias and precision loss when it models intermediate outcomes incorrectly, and hence fails to use the post-randomization information harmlessly. This paper proposes an extension of the commonly used MMRM, called IMMRM, that improves the robustness and optimizes the precision gain from covariate adjustment, stratified randomization, and adjustment for intermediate outcome measures. Under regularity conditions and missing completely at random, we prove that the IMMRM estimator for the average treatment effect is robust to arbitrary model misspecification and is asymptotically equal or more precise than the analysis of covariance (ANCOVA) estimator and the MMRM estimator. Under missing at random, IMMRM is less likely to be misspecified than MMRM, and we demonstrate via simulation studies that IMMRM continues to have less bias and smaller variance. Our results are further supported by a re-analysis of a randomized trial for the treatment of diabetes.

 **TUESDAY AFTERNOON WORKSHOP (1:30 pm – 4:30 pm)**

**A. (CLINICAL) Modern Bayesian Approaches to Using Historical, Auxillary, and Real World Data in Drug Development**

 **Organizer/Chair: Brad Carlin, PharmaLex**

1. Bayesian nonparametric models for early-phase clinical trials

 **Speaker: Yuan Ji, University of Chicago**

**TBA**

2. Complex Innovative Design using a Master Protocol for Chronic Pain

Speaker: Phebe Kemmer, Eli Lilly

In September of 2019, Eli Lilly and Company announced that the FDA had accepted its application to the Complex Innovative Trial Designs (CID) Pilot Meeting Program. The trial accepted into the CID program is a phase 2 master protocol in chronic pain, a condition that can cause limitations in general activities and daily living and can tremendously burden the patient, family, and caregivers. The chronic pain master protocol will efficiently evaluate the safety and efficacy of multiple assets in multiple pain types. A key feature of the master protocol is to balance the standardization of design elements where possible, while still allowing for the flexibility to meet the needs for each asset that may enter the master protocol. The statistical model used in the design allows for the borrowing of key statistical information between assets and pain types, either through the pooling of data or through more sophisticated approaches such as Bayesian hierarchical modeling. During this talk, we will provide an overview of the design, including both the challenges and opportunities of conducting a master protocol along with some key learnings on the implementation.

3. Indirect Treatment Comparisons: When Are They Needed and How Do They Work?

Speaker: Haitao Chu, Pfizer

In many markets, gaining approval by national reimbursement, pricing, or health technology assessment agencies is critical to the commercial success of a new product launch. In the absence of direct evidence from head-to-head RCTs, private and national payers often expect to see evidence from indirect treatment comparisons including Bucherâ€™s method, network meta-analysis (NMA) or population adjusted indirect comparison (PAIC) to demonstrate the clinical value of the new technology. In this talk, I will provide an overview on indirect treatment comparisons focusing on when are they needed and how do they work? In addition, we will discuss the assumptions, advantages, and disadvantages of each approach. In practice, it is important to consider multiple approaches as sensitivity analyses and to provide totality of evidence as indirect treatment comparison is at high risk of bias no matter which approach is chosen. This is a joint work with Zheng Wang, Zilin Wang, Yong Chen, Lifeng Lin and Joseph C Cappelleri.

4. Opportunities for new estimands in clinical trials through principal stratification

 **Speaker: Patrick Schnell, Ohio State University**

Principal stratification defines subgroups based on post-randomization variables such as compliance, adverse events, disease progression, or death. It has gained popularity as one approach to defining estimands in the presence of intercurrent (post-randomization) events in part due to recent FDA guidance. In addition to offering rigorous approaches to well-known problems, principal stratification can also be used to obtain new information from clinical trials with very basic designs. We will describe two secondary analyses of clinical trial data using principal stratification. First, we will examine how effects on patient perception of benefit from duloxetine for treating aromatase inhibitor-associated arthralgias (e.g., joint pain from anti-cancer hormone therapy) vary depending on whether duloxetine would cause (versus placebo) adverse events and improvements in pain. Second, we will determine whether patients starting a treatment for insomnia have a positive expected benefit from continuing (versus discontinuing) after observing an early response or lack thereof. Both questions are addressed using data from simple parallel arm trials without special features (e.g., planned treatment discontinuation). In each case, necessary assumptions and methods for identifying causal effects will be described.

**WEDNESDAY MORNING WORKSHOP (8:30 am – 11:30 am)**

**A. (CLINICAL) Statistical Challenges and Solutions for Decentralized Clinical Trials**

 **Organizers/Chairs: Karen Liu, Eli Lilly**

1. Impact of Using A Mixed Data Collection Modality on Statistical Inferences in Decentralized Clinical Trials

**Speakers: Alex Curtis and Yongming Qu, Eli Lilly**

Decentralized clinical trials offer the promise of reduced patient burden, faster and more diverse recruitment,

and have received regulatory support during the COVID-19 pandemic. However, lack of data accuracy or data validation poses a challenge for fully decentralized trials. A mixed data collection modality where onsite measurements are collected at key time points and decentralized measurements are taken at intermediate time points is attractive operationally. To date, the impact of decentralized measurements (which could presumably be less accurate) taken at intermediate time points on statistical inference on the primary or other key time points has not been evaluated. In this research, we evaluate the estimation and statistical inference for three scenarios: (1) all onsite measurements, (2) a mixture of onsite and decentralized measurements, and (3) all decentralized measurements, in the setting of a chronic weight management trial. We consider scenarios where decentralized measurements have additional within- and between-subject variabilities and/or bias. Simulation studies showed that in the mixed modality setting the estimation and inference for the key time points with onsite measurements have good properties and are not impacted by the additional variability and bias from intermediate decentralized measurements. However, estimates for intermediate decentralized time points for the mixed modality and estimates for all decentralized modality measurements have increased variability and bias. In conclusion, mixed modality trials can help achieve the benefits of decentralized clinical trials by reducing the number of onsite visits with little negative impact on statistical inferences for various estimands, compared to traditional (all onsite) clinical trials.

2. Evaluation of the effect of centralized reader on Alzheimer's Trials

**Speakers: Melissa Williamson and Dunlei Cheng, Eli Lilly**

**TBA**

3. Remote Data Collection using Digital Health Technologies in Clinical Development

**Speaker: Jie Shen, AbbVie**

Digital health technologies (DHTs), such as wearables, smartphones, and other digital devices, have been widely used in clinical trials and many healthcare application scenarios. They provide opportunities for remote data collection and therefore serve as an important piece for decentralized trials. This presentation will start with the importance of digital health technologies and their potential benefits for clinical development. Current regulatory guidance related to remote data collection will also be reviewed. The presentation will also highlight the uniqueness of digital data analytics with examples of digital measurement development and validation. Finally, challenges in data analytics will be discussed, including issues related to data quality, data integration and missing data handling.