Eli Lilly 2018 Statistics Internship Opportunity

Project Descriptions

1. **Project title: Study designs for individualized dose treatment – PhD candidate**

Tailored or individualized treatments become more and more important in health care. There are two levels of tailoring in adjusting for treatments or doses: (1) treatments/doses are assigned based on prognostic or genetic factors; and (2) treatments/doses are adjusted based on early response. For example, in initiating basal insulin treatment for patients with type-2 diabetes, the initial basal insulin dose may be determined by body weight and/or baseline fasting glucose. Then, basal insulin doses are adjusted according to the glucose response on a weekly basis. In the end, the insulin doses are fully individualized. On the other hand, for most medications, there are only 2 or 3 dose strength available and the doses are not individualized. It is well known that the responses to a treatment/dose could vary greatly for different patients and the approach of one size fitting all may not achieve the best outcome (e.g., the optimal balance of efficacy and safety/tolerability). Therefore, it is critical to explore the possibility of individualizing the non-insulin diabetes treatments to maximize the efficacy while minimize the tolerability/safety. The project will create scenarios through theoretic modelling and simulations to demonstrate the feasibility and benefit of individualized flexible dosing titration. A white paper or a manuscript will be developed to provide guidance on developing flexible dose regimens.

2. **Project title: Alternative approaches to non-responder imputation for a binary composite endpoints – PhD candidate**

Composite endpoint is quite common in clinical trials (UC). For instance, the primary endpoint of treating ulcerative colitis is a binary variable of clinical remission, which can be defined based on three components including stool frequency (SF), rectal bleeding (RB) and endoscopic subscore (ES). The current regulatory-required analysis method for this primary endpoint is Cochran-Mantel-Haenszel (CMH) chi-square test together with the non-responder imputation (NRI) approach to handle missing data. The NRI approach implies that a patient will be considered a non-responder if one of the 3 components is missing due to any reasons. The NRI approach is deemed conservative but may introduce bias in favour of placebo, and the power by the CMH test may be decreased by ignoring the partial data, e.g. some components are observed and some others not. In addition, the components of SF and RB will provide longitudinal data as they are easier collected than the component of ES, which is often only collected at the endpoint time point. Therefore it is further challenging of fully utilizing the early collected SF and RB data to predict missing endpoint components and then further predict the missing primary composite endpoint.

To solve these issues, we propose two alternative approaches to NRI. The first one is to use multiple imputation technique in which missing components of a patient are first imputed by non-missing components via likelihood inference of observed data from all patients under the assumption of a reasonable missing mechanism, such as MAR. The composite status of the patient can then be derived from the completed components. The second one is a joint

modelling approach within generalized linear model framework, in which we simultaneously analyse the composite endpoint together with its three components. The missing data in the components will be handled by the correlation structure between endpoints. The two proposed alternative approaches will be compared to the traditional CMH tests with NRI through simulations and illustrated with a real data analysis.

3. **Project title: Clustering longitudinal data to explore underlying patterns in patient responses that may be associated with clinical or demographic characteristics – PhD candidate**

Pharmaceutical clinical trials typically measure clinical outcomes at multiple time points to assess the treatment effect over these outcomes in terms of disease progression and response to intervention. The typical estimation procedure used for the treatment effect has been to analyze the outcomes using parametric longitudinal models, e.g., Mixed-Model Repeated Measures (MMRM), because it also implicitly addresses missing outcomes through the Missing-at-Random (MAR) assumption. However, it is quite common for these longitudinal trajectories to exhibit great noise even after for controlling for key covariates (e.g., baseline values and dose levels). Moreover, this procedure is hinged on the assumption that the outcomes are normally distributed -- something that regulatory agencies, particularly the FDA have continually challenged both because of the normality assumption and whether it is effective in handling missing data. Corollary to this is the inability of this method to assess, while perhaps exploratory, whether there are differential patterns of longitudinal response in an unsupervised way.

We propose assigning multivariate Dirichlet process (DP) priors on the random intercepts and slopes within a mixed effects model on the response. These priors will facilitate clustering while controlling for covariates or even adding a latent structure that the clustering is dependent on the covariates as well. Missing data methods will be explored as appropriate. Simulations are planned to assess the performance of our model.

4. **Project title: Variance Estimation and Common Support for Treatment Comparisons using Generalized Propensity Score Matching – PhD candidate**

In comparative effectiveness research using observational study data, conventional propensity score adjustment is the gold standard in the case of 2 treatment groups. However, it has significant limitations when applied in setting with >2 treatments (such as a lack of common support when applied in a pairwise fashion). Thus, there is no gold standard method for bias control in the multi-treatment observational studies. A new method, generalized propensity score matching, was recently developed (Yang et al. 2016. Propensity score matching and subclassification in observational studies with multi-level treatments. Biometrics 72(4):1055-1065). The approach extended standard propensity score methods to cases with > 2 treatment groups – a common setting for observational comparative effectiveness research. It allows for comparisons across multiple treatments using a common support while removing bias from observed covariates under the 'no unmeasured confounding' assumption. While the theoretical basis for the new approach has been set, establishing best practices surrounding implementation and resolving challenges regarding variance estimation and establishing a common support are needed before widespread application is possible. Once best practices surrounding the use of this new approach are resolved, it has many potential applications in

comparative observational research. Goal: The objective of this research is to establish best practices surrounding the use of generalized propensity scoring, specifically setting standards for obtaining common variance estimate, assessment of an optimal common support with sufficient overlapping in the covariate space, and assessment of covariate balance. In addition, a SAS program package will be developed for implementation.

5. Project title: Intelligent titration algorithm for basal insulin PhD candidate

Basal insulin therapy is one of the most efficacious treatment among all glucose-lowering agent for diabetes patients. Due to the adverse event associate with basal insulin, such as hypoglycemia, the physicians, as well as the patients themselves, are often reluctant to initiate and adjust insulin therapy. Insulin titration algorithm is a vital component for the success of insulin initiation and optimization. Improving upon the available titration algorithm of basal insulin will have tremendous impact on the success of future clinical programs and the improvement of patients' health outcome. The intern for this project will explore various model based control systems (PID and MPC) and develop an intelligent basal insulin titration algorithm. This algorithm should be able to automatically provide individualized insulin delivery guidance and have online learning ability. The goal is to help insulin user achieve the best glucose control within minimum time interval and less hypoglycemia. It could potentially be used in our future clinical development program. The intern will also have the opportunity to interact with highly interdisciplinary functional expert from various therapeutic areas to broaden perspective and maximize utility of the algorithm.

6. Project Title: Design for combination therapy - PhD candidate

Researchers in pharmaceutical industry are exploring various methodologies to improve the speed and increase success in early phase dose-response studies, as proper dose selection is a vital component of a successful drug development program. Improving upon the available statistical methodology in this area can have a great impact on the success of future clinical programs.

As part of the development strategy for a molecule, the use of combination therapies with another molecule is believed to lead to treatment synergies that result in improved efficacy, and hopefully to differentiate from other small molecules or biologic agents. However, challenges exist because these two investigational drugs have not had their optimal dose combination determined via clinical studies, and the total number of treatment combinations to be tested in a dosing-ranging study will be large. How to design an optimal trial to test all doses using limited number of total patients (which is often restrained by the project budget for a phase 2 study) to identify the best dosage(s) in the combination therapies to inform phase 3 studies will be a motivating example in this project.

Under this setting, the Bayesian Response-Adaptive Randomization (RAR) approach where the randomization ratio is altered at interim analyses according to subject response data among the treatment groups can be extremely useful. This approach can be applied to allocate more subjects to dose combinations with a higher probability of a treatment related efficacy response or to maximize the information gain on dose-response.

There are several key recommendations resulting from this project:

1. Identify the proper statistical model to be applied to the constraints of this study, which models the dose-response of monotherapies and dose combinations. Thereby, enabling optimal borrowing across combinations within our study.

2. Identify the proper quantitative metrics for within study adaptations. Such model-based metrics will be used to eliminate/add dosing groups and modify the randomization ratios.

3. Identify key design features such as the size and frequency of interims, total study size, etc.

These recommendations will be formulated based on extensive simulations. Simulations of a balanced factorial design will be performed for comparison.

The intern for this project will explore various models through trial simulation and theoretical development geared at providing statistical guidance/strategy per relevant clinical settings. The intern will have the opportunity to interact with highly interdisciplinary functional representatives involved in clinical development (as well as researchers from various therapeutic areas) to broaden perspective and maximize utility of the project's conclusions.

7. **Project Title: Advanced Statistical Modeling in R – Unleashing the Tidyverse on Clinical Analyses – Master candidate**

SAS is currently the dominant statistical programming language at Lilly and in the pharmaceutical industry. However, the continual and rapid development pace of open source languages (e.g. R and python) has challenged this position. The goal of this project is to demonstrate how R's latest modelling paradigm can greatly increase the power and flexibility of Lilly's clinical analysis pipeline. A package will be developed based upon R's tidyverse framework. This framework naturally supports a broad range of models, from routine frequentist statistical methods to more advanced modelling approaches (Bayesian methods and machine learning). This project will provide reusable code spanning this set of models to eliminate technical barriers to migrating away from a SAS based pipeline. In addition to technical code-based solutions, this internship will survey Lilly's SAS and R communities to explore Lilly cultural factors driving SAS usage. The package will be developed and published in conjunction with Lilly modelling and R experts providing guidance on modelling and R package development best practices. The successful intern should have strong R programming skills and some understanding/experience with the tidyverse and related R packages (e.g. dplyr, tidyr, tibble, purrr, modelr, broom, ggplot2). If necessary, they should be willing to learn and adapt their R programming style to fit into this paradigm. Additionally, since there of this internship that involves meeting with statistical programmers and asking them their thoughts on SAS versus R, the intern should be comfortable meeting with others in a 1:1 setting and networking within the statistics community at Lilly.