



Eli Lilly and Company 2021 Summer Intern Project Description

Project Title: Leveraging Treatment Effect Information across Indications to Improve Decision Making in Pain Master Protocol – PhD candidate

Chronic pain is one of the most common debilitating condition that impacts millions of people in their daily lives. The chronic pain master protocol provides the infrastructure to evaluate multiple assets as well as to determine their efficacy and safety in three different pain types – osteoarthritis, chronic lower back pain and diabetic peripheral neuropathy pain. With the availability of cross indication data for a single asset, there is an increasing need to understand homogeneity of the treatment efficacy across pain types within an intervention and if borrowing treatment effect information cross indications would improve the signal detection and thus facilitate better portfolio level decision making.

This project is motivated by the following research questions: How can we best evaluate the exchangeability of a drug performance in multiple related disease conditions? What level of exchangeability would be required in order to borrow treatment effect information across indications?

The goals of this internship project are to understand the framework of chronic pain master protocol; review the existing/curated literature in pain space to get a basic understanding of the drug efficacy across indications; review the available network meta analyses in each pain condition and explore the option of performing a cross indication network meta-analysis to inform exchangeability across indications; evaluate the existing Bayesian methods in literature to propose a treatment effect borrowing methodology that suits the framework of the pain master protocol; identify the potential risks in treatment effect borrowing across indications and provide some insights on the limitations in proposed approach; and implement method and develop R function\Shiny App for broader usability at Lilly as needed.

Project Title: FMA framework for Estimating Casual Treatment Effects for Observational Real-world Data with Survival Endpoints – PhD candidate

Lilly statisticians have developed a model averaging framework for estimating the average treatment effect (ATE) for observational comparative effectiveness studies with continuous outcome (manuscript in revision). This framework is designed to incorporate model uncertainty into the analysis of treatment choice and outcome as opposed to the traditional approach of using a single model to assess the ATE. Numerous methods are used for modeling treatment choice and outcome, many of which are modern machine learning methods. Also included are the standard approaches. The averaging of a large suite of ATE estimates has been found to perform well in simulations and is a major advance in analysis of observational CE studies which will provide better answers for our CE studies with continuous outcomes. The model averaging framework is currently being modified to accommodate binary outcomes, but it is less obvious how to proceed for estimating the counterfactual outcomes and model-specific weights for the FMA estimator with survival endpoints. We would like a summer intern to focus on evaluating the appropriate estimand for survival endpoints (such as based on the median survival or restricted mean survival), the suite of models/methods for modeling the outcome, the estimation of the counterfactual outcome, and the methodology to estimate weights for averaging estimates from individual models.



Eli Lilly and Company 2021 Summer Intern Project Description

Project Title: Estimand and Estimation of Win Ratio: An Alternative Approach to Analyze Composite Endpoint Using Simulation —PhD Candidate

A composite endpoint as the primary endpoint is widely used in clinical trials across therapeutic areas. However, conventional statistical methods for composite endpoints bears a major limitation of ignoring the clinical priorities among the components.

The win ratio method (Pocock et al. 2012) has been gaining popularity recently with two advantages: 1) leveraging relative clinical importance among all components; 2) offering flexibility by incorporating endpoints with various types. This approach has been applied in Phase 3 study designs to support registration. However, early dropouts typically result in ties under the win ratio framework. In addition, patients may have missing data for certain components of the composite endpoint. Both cases need simulation to address their impact on estimation.

This project intends to describe the imputation process using three hierarchical endpoints via simulation: time to death, time to first hospitalization/clinical visit due to certain clinical event, number of hospitalization/clinical visit due to this clinical event, and a continuous endpoint which could be further grouped into dichotomous endpoint.

Project Title: Matching and Analyses in Non-randomized Studies - PhD candidate

Real-world evidence becomes more and more important for drug development and commercialization. Matching is an important technique in non-randomized studies to evaluate the difference in outcome between treatments or disease status (with or without a disease). We need a clear guidance on how to perform matching and the corresponding analyses. The most used matching method is the propensity score matching, where propensity is the probability of treatment selection modeled via baseline covariates. However, matching by propensity has been criticized on several accounts. On the other hand, matching on all baseline covariates through some distance measures may not produce a good match because of the high dimensionality of covariates (the “curse of dimensionality”). Some literature suggests utilizing the prognostic score matching based on a reference treatment (see the work by 2020 summer intern Yunshu Zhang). The prognostic score matching enables a better utilization of important covariates, and recent simulations showed good results under scenarios of homogenous treatment effect. However, under treatment effect heterogeneity when the relationship between baseline covariates and the outcome is different across treatment arms the advantages of prognostic score-based matching are not clear. Additionally, estimators of treatment effect based on matching are a non-smooth function of the data and the validity of many statistical methods for variance estimation (such as delta methods and bootstrap) may be questionable. This summer intern project will aim to identify a new method in matching and analysis that outperform existing methods in literature.

Project Title: A Systematic Evaluation of Supervised Methods for Cell-type Classification from Single-cell RNA-seq Data - PhD candidate

Single cell RNA sequencing (scRNA-seq) has the advantage of measuring genome-wide transcript expression for individual cells. It is complementary to bulk RNA-seq. By profiling individual cells, scRNA-



Eli Lilly and Company 2021 Summer Intern Project Description

seq can identify different cell types and facilitate target identification by providing cell type specific gene expression. The current cell-type assignment module is prior knowledge-driven and requires manual labelling. To make it automated, we will evaluate currently available methods that are based on popular machine learning classifiers. Some classifiers incorporate a rejection option, leaving a few cell populations unlabeled, to identify novel cell types in the test set that were not seen during training. To choose the method with the best overall performance across different experiments, we are going to train and test the classifiers using scRNA-seq datasets of different sizes, species, tissues and levels of complexity. Finally, a cell-type classification module will be added into our existing single cell data analysis pipeline.

Project Title: To develop a Bayesian Hierarchical Model That Accounts for Correlation within Mechanism of Actions, Indications, and Endpoints, Along with the Standard NMA Sources of Variability - PhD candidate

Bayesian network meta-analysis (NMA) is a core capability at Lilly, contributing to design and decision making throughout the drug development process. In many therapeutic areas, the effects of drugs over different mechanism of actions are investigated in several indications and endpoints. With multiple drugs in the pipeline targeting different pathways, one question that arises is which indication to prioritize. We propose to extend currently used Bayesian NMA models for the cases of different endpoints and indications. The primary goal will be to develop a Bayesian hierarchical model which accounts for all of the correlation (mechanism of action, endpoints, indications) along with the standard NMA sources of variability (within study, between study). The benefits include inclusion of more comparator drugs into the network meta-analysis models and allows for prediction of how a drug will work in other indications or endpoints conditional on the information we have. The intern's responsibilities will include developing the model with a read dataset and examining the statistical properties of the resulting inferences.

Project Title: Improving Robustness and Precision in Estimating the Drug's Effect on Delayed Response in Diabetes Early Phase POC Study via Efficient Borrowing of External Information - PhD candidate

In Diabetes Proof-of-Concept (PoC) study, the most critical endpoints are daily mean blood glucose and body weight change from baseline at certain time point, say week 12. These are called delayed response as time is needed to show drug's effect. Methods have been developed by Lilly statisticians to model the effect of drug on these delayed responses. For example, Fu and Manner (2010) have developed ITP model, a parametric longitudinal model, to characterize the time profiles, e.g., of body weight change over time, that could be well approximated by an exponential decay pattern; Qu (2019) developed a proportional discrete time (PDT) model to provide approximation to the daily mean blood glucose change while Qu et al (2019) extended the above models to take into account the modelling of pre-planned dose titrations. Despite these progresses being made, it remains the case that the modelling is being implemented based on the investigated PoC study alone, whether it is simulation or analysis, without considering the information from similar compounds that are readily available. Borrowing information from similar compounds or compounds from the same class may potentially increase robustness and precision in estimating the treatment effect. Additionally, it makes sense in that the similar compounds are also likely to share similar rate of change in these delayed responses over time. Therefore, this project was proposed to develop a framework for a robust information borrowing to augment a PoC study in Diabetes



Eli Lilly and Company 2021 Summer Intern Project Description

with historical data. Some possible approaches include power priors with dynamic powers determined by the extent to which the external data is consistent with the investigated study, or a meta-analysis approach based on Bayesian hierarchical random-effects models. This novel augmentation framework leveraging historical information could provide the goals of (i) robust prediction of drug performance in a longer term (e.g., from 12 weeks (PoC) to 26 weeks (Phase 2)) and (ii) robust subsequent designs during the early phase clinical development

Project Title: Analysis of Paired Time-to-Event Data - PhD candidate

With target agents increasingly being the focuses in oncology drug development it's becoming more common that single-arm trials support regulatory approvals. Lack of pre-defined and/or clinically relevant hypotheses to define clinical benefit and lack of reference for comparison are among known limitations leading to multiple challenges during the regulatory review process, launch readiness, and reimbursement negotiation. A proposed solution is to use each study patients as his/her auto-control and to use prior data of each study patients as a clinically relevant reference for comparison.

The current project will focus on technical details of the analysis of paired response or time-to-event data (e.g. PFS on the last line of therapy prior to study enrolment vs PFS on investigational drug). The project will include literature review to get a comprehensive overview of existing methodological approaches, conducting a simulation study to assess their performance under various assumptions, exploration of appropriate endpoints and testing frameworks, and developing recommendations for future use. If time allows, the project will continue with developing a macro or a program template for the recommended option(s), and applying these approaches to data from previous randomized trials, in order to contrast outcomes based on auto-control comparisons to those generated from typical treatment group comparisons.

Project Title: Novel Evidence Synthesis Methods: Developing Matched Historical Controls to Support Pediatric Extrapolation and Enhanced Decision Making - PhD candidate

The goal of this internship is to further Lilly's ability to leverage external information to inform trial design and data analysis. Methods will focus on synthesizing and borrowing patient-level data to facilitate pediatric extrapolation. The intern will compare various methodologies, which will be prioritized to deliver on 2 Innovation Projects (pediatric innovation, and borrowing external information), deliver code and an application so that after the internship is complete the methodologies are easy to implement and describe for trial design, simulation, and regulatory communication. The intern will apply these methods on current portfolio projects to improve decision-making and lead to more successes at leveraging historical data in our pediatric plans, and early and late phase clinical trials.

Project Title: Evaluation of Doubly Robust Methods for Estimating Casual Treatment Effects on Observational Real-world Data - PhD candidate

Observational cohort studies are increasingly being used for comparative effectiveness research (CER) and to assess the safety of therapeutics. To address the issue of confounding due to lack of covariate balance across treatment cohorts in observational studies, we compared the performance of several



Eli Lilly and Company 2021 Summer Intern Project Description

matching estimators in estimating average treatment effects (ATE) including propensity score, prognostic score and double score matching (matching on both propensity score and prognostic score, DSM) as part of RWA intern's project in 2020. We found that double score matching (DSM) estimators of the ATE outperformed single propensity score or prognostic score estimators. As the next logical step of the research done by our 2020 intern, we propose the 2021 summer internship project focusing on evaluating the use of doubly robust methods by matching, weighting or regression. The key advantage of the doubly robust estimators is that they require only one of the two models (one for treatment and one for the outcome) to be correctly specified to obtain an unbiased estimator of ATE, and therefore can lead to more accurate and often also more precise inference. In addition to DSM, currently there are other doubly robust estimation methods in the statistical literature including augmented inverse propensity weighted (AIPW), outcome regression based on penalized spline of propensity methods for treatment comparison (PENCOMP), and targeted maximum likelihood estimation (TMLE) (Ju et al. 2020; Dorie et al. 2018). The AIPW estimator improves on the IPW estimator by fully utilizing the information about the probability of treatment as well as the predictive information about the outcome variable (Glynn et al. 2010). That is a combination of the basic IPW estimator and a weighted average of the outcome regression estimators. The PENCOMP was proposed using a robust multiple imputation-based approach to causal inference (Zhou et al. 2019). PENCOMP estimates causal effects by imputing missing potential outcomes with flexible spline models including a penalized spline of the logit of the propensity score with fixed knots and a parametric function of other covariates predictive of the outcome, and then draws inference based on imputed and observed outcomes. However, to the best of our knowledge, little work has been done to understand the challenges of covariates selection in model, overlapping of the covariate distribution, diagnostics, and performance of these doubly robust estimators at Lilly and statistical community. In addition, it is unclear how the addition of doubly robust methods into our model averaging comparative effectiveness analyses can improve the performance of this machine learning approach. The goals of this project are to examine the relative performance of different doubly robust methods for estimating casual treatment effects, understand how the addition of doubly robust methods can influence our model averaging approach, and develop sound guidance on the best practices for applying doubly robust estimation in observational data settings through theoretical proofs and simulations. The intern will begin with a literature review of doubly robust methods and assumptions followed by mathematical proofs, and extensive Monte Carlo simulations under different scenarios mimicking real world data to evaluate the value of doubly robust estimators. To support the best practices, these doubly robust methods will be implemented in an R package and/or SAS macros.

Project Title: Competitive Intelligence Tracker Dashboard – Master candidate

Competitive intelligence (CI) can help us stay ahead of the competition. It is a very critical component in the process of drug development in that a timely competitive landscape analysis could help not only with efficient and informed design of future clinical studies but also could enable us to bring the drug to the market or to terminate the drug with more confidence. Clinicaltrials.gov is one of the main sources for this information. The current practice of CI office is to frequently check and manually maintain the most recent information. The objective of this project is to build a platform to make this process dynamic and more effective. The intern will work to create this platform to access the online information via API in real time, add meaningful competitive analytics and then present them through effective visualization in an easy interactive dashboard (e.g., R flexdashboard). By doing this, the platform is enabled to provide real-time CI for drug development.



Eli Lilly and Company 2021 Summer Intern Project Description

Project Title: Cloud Computing for Clinical Trial Simulation– Master candidate

Clinical trial design choices such as sample size, interims, doses, and stopping rules depend on computationally intense simulation studies for justification. Workflows need to produce results in a timely manner, not only for internal decision-making, but also in external interactions with regulatory authorities, where it becomes necessary to share a common computing environment. After the computation finishes, the results should be cleanly documented and archived so teams can retrieve old work and communicate the original reasoning. Enduring solutions to these challenges must anticipate the changing landscape of high-performance computing, where there is a steady inexorable shift away from traditional private computing clusters towards publicly available enterprise cloud services like AWS, Google Cloud, and Azure. This summer internship will explore improvements to the shelf life, traceability, and discoverability of simulations. The intern will design a cloud-based storage system to archive and standardize simulation projects so clinical teams can search previous work, follow the inferential paths leading to existing designs, and recover large data artifacts. In addition, the intern will explore ways to seamlessly execute existing R-focused simulation projects on cloud-hosted computing environments that regulatory authorities could potentially access

Project Title: To Develop an Optimal Design Methodology for Bioassay Dilution Scheme– Master candidate

The purpose of this internship is to develop an optimal design methodology for bioassay dilution schemes. The dilution scheme plays a critical role in the quality of relative potency estimation for bioproducts. The internship will require evaluating and comparing various nonlinear optimal design strategies, including Bayesian options (e.g.: using approximate coordinate exchange algorithm), with the goal of recommending an approach that is compatible with the current Lilly method control framework. The project will consider the impact of the optimal dilution scheme on control measures such as goodness of fit, statistical similarity between reference and test sample curves, and relative potency precision and accuracy. There will be an expectation to partner with bioassay scientists and statisticians. An external publication of the work is also a possibility.

Note: Additional MS Projects are pending confirmation that aim to provide you with practical experience at Pharmaceutical industry.

Strongly encourage you to apply by Jan 1st (PhD, [link](#); Master, [link](#))