MEDICAL UNIVERSITY OF VIENNA

Wiener Biometrische Sektion
der Internationalen Biometrischen Gesellschaft
Region Österreich – Schweiz

Please save the date for the Summer Biometric Seminar 2024

BRIDGING THE GAP BETWEEN BAYESIAN & FREQUENTIST APPROACHES IN CLINICAL TRIALS FOR DRUG DEVELOPMENT

When? **June 21st 2024, 09:00 – 12:00 CET**

Where? **In person: Jugendstilhörsaal of the Medical University of Vienna**
Spitalgasse 23, 1090 Vienna
Online: Via Webex. Please send an email to elias@berryconsultants.net to register.

ABSTRACT

Adaptive designs and complex clinical trials offer many well-known advantages throughout the clinical development process and their acceptance is steadily increasing. Typically, such designs use either the Bayesian or the frequent framework for decision-making and reporting. While frequentist adaptive designs often have closed-form calculations of operating characteristics, Bayesian designs usually require simulations. On the other hand, Bayesian designs often make it easy to communicate results, incorporate multiple endpoints and achieve efficiency gains by using e.g., the predictive probability for interim decision making. Regardless of the choice of analysis method and the associated philosophical differences in the paradigms, there is an understanding that, among others, frequentist operating characteristics such as power and type 1 error are important to evaluate the proposed design. Ultimately, both Bayesian and frequentist adaptive designs aim to and should be judged by their ability to produce better and more efficient clinical trials without compromising their statistical integrity. In this session, we will bring together experts in the design of both Bayesian and frequentist adaptive trials to learn more about recent methodological advances, regulatory considerations, and practical experiences when designing and assessing these trial designs.

Confirmed Speakers:

- Cora Allen-Savietta, Berry Consultants
- Nicholas Berry, Berry Consultants
- Amy Crawford, Berry Consultants
- Florian Klinglmüller, Austrian Agency for Health and Food Safety
- Martin Posch, Medical University of Vienna
- Rainer Puhr, Monash University

Organizers: Franz König, Medical University of Vienna, Elias Laurin Meyer, Berry Consultants

PROGRAM

09:00 – 10:20: Session 1

- Amy Crawford: Anticipating a heterogeneous treatment effect: Bayesian modeling in the STEP trial
- Cora Allen-Savietta: Predictive Probabilities Made Simple: An Intuitive and Accurate Method for Adaptative Clinical Trials
- Rainer Puhr: BATS - The Bayesian Adaptive Trial Simulator

10:20 – 10:40: Coffee

10:40 – 12:00: Session 2

- Nicholas Berry: Modelling of Time Trends in the PRINCIPLE Platform Trial
- Martin Posch: Bayesian and frequentist approaches to incorporate non-concurrent controls in platform trials
- Florian Klinglmüller: Challenges when using external control data for regulatory decision making

INDIVIDUAL ABSTRACTS

Cora Allen-Savietta

Predictive Probabilities Made Simple: An Intuitive and Accurate Method for Adaptative Clinical Trials

Dr. Cora Allen-Savietta (Berry Consultants) will explore the benefits of Bayesian predictive probability algorithms for optimal dose selection, subgroup enrichment, and adaptive trial sizing in both Bayesian and frequentist clinical trial designs. Bayesian predictive probabilities are a powerful tool because they account for the current uncertainty in key trial parameter estimates and future uncertainty in those parameters, can leverage external information or multiple endpoints, and, crucially, consider the size of future, unknown data. Combining all this information leads to better decision-making and more efficient trials.

Despite their usefulness, calculating Bayesian predictive probabilities can be a significant challenge, especially in trial design simulation. In her talk, Cora will introduce a predictive probability approximation using either a p-value or a posterior probability that significantly reduces this burden.

Nicholas S. Berry

Modelling of Time Trends in the PRINCIPLE Platform Trial

Modeling time has dramatic impacts on a platform trial. If we are able to account for changes over time in a platform trial, often years or thousands of patients worth of data become available to inform current analyses. If we are unable to account for changes in time, those same extra data can create biased estimates and poor operating characteristics for tests. It is vital to assess the required assumptions for using past data and to verify whether those assumptions are satisfied in practice.

The PRINCIPLE platform trial in COVID-19 enrolled over 11,000 participants across the UK between April 2020 and July 2022. Randomization in the trial began shortly after the virus emerged and, not unlike the flu virus, experts suggested that it was likely to evolve over time. To accommodate the likely evolution, the PRINCIPLE primary analysis includes an adjustment to measure and account for changes in the disease over time.

Few platform trials have completed accrual, and the PRINCIPLE trial is likely unique in being a completed platform trial with a pre-specified time adjustment in the primary analysis model. In the primary analysis, each participant receives a time adjustment based on their randomization date. The pre-specified adjustment comes from a Bayesian time machine that smoothly models differences across time. Adjustments of this nature allow for a fair comparison of participants enrolled at different times over the tenure of the trial.

As anticipated, the model estimates reflect clear trends in the COVID-19 recovery outcomes over time.

In this talk, we will go through a deep exploration/retrospective of the time based results from the PRINCIPLE trial. We will show results from the platform trial, and walk through how the COVID-19 virus evolved in the UK, as captured by the model. We provide model results, interpretable figures, and possible explanations of the observed time trends from the Bayesian model. Additionally, we will describe alternative methods of handling time trends - the concurrent analysis model and the time categorical model. We compare the Bayesian Time Machine model results in PRINCIPLE to those alternative models to determine if differences in decisions or estimates would have been observed if those models were used.

Amy Crawford

Anticipating a heterogeneous treatment effect: Bayesian modeling in the STEP trial

Pivotal trials have established endovascular therapy (EVT) as a safe and highly effective treatment for a relatively narrow range of acute ischemic stroke patients. The therapy is administered based on characteristics of the stroke such as location and severity (e.g. NIH stroke scale) and initial EVT studies targeted patients with stroke characteristics thought to maximize the observed benefit. There remains uncertainty about the full patient population who should receive the therapy and it is probable that patients outside this narrow range will also benefit. The StrokeNet Thrombectomy Endovascular Platform (STEP) trial is a platform trial designed to optimize care for acute ischemic stroke patients. The first research question in the platform trial will explore expanding the indication of EVT to patients with stroke characteristics outside of the established efficacy population.

The study will enroll patients with strokes that are not included in the current indication for EVT. We expect the effect of EVT to diminish as the stroke severity, measured by NIH stroke scale, deviates from the original study populations. We wish to understand the NIH stroke scale value where EVT is no longer superior to medical management alone. For this applied problem, Dr. Crawford will present a Bayesian modeling framework that searches the space of baseline stroke characteristics to find an appropriate population for indication expansion, if one exists. The research question is naturally answered in the Bayesian framework, incorporating prior knowledge of approvals for the therapy and knowledge of the biological process.

Florian Klinglmüller:

Challenges when using external control data for regulatory decision making

In settings where the conduct of a randomized controlled trial is challenging, use of external control data - including real-world data - is frequently proposed to support conclusions about the efficacy of new treatments. The predominant approaches to incorporate external control data include various types of Bayesian borrowing and causal inference methods based on propensity scores. While these methods come with a promise to provide useful insights and potentially reduce bias, they add complexity to pre-specification and rely on additional assumptions that are often not transparent (EMA (2023)) . Consequently, the substitution of internal with external control data requires compelling justification, as it introduces additional uncertainties and potentially compromises internal and external validity.

We present a review of EMA scientific advice letters discussing proposals to use external control data to either augment the (internal) control arm of randomized trials or serve as the sole control arm to a single arm trial. We present results on the frequency of proposals with respect to study design, indication, and statistical methods to address various sources of bias. Furthermore, we summarize common positions and concerns in the scientific discussion of the identified advice letters and highlight the resulting regulatory challenges.

EMA (2023) - Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation (EMA/CHMP/564424/2021).

Martin Posch:

Bayesian and frequentist approaches to incorporate non-concurrent controls in platform trials

Platform trials evaluate the efficacy of multiple treatments, allowing for late entry of the experimental arms and enabling efficiency gains by sharing controls.

The control group in platform trials consist of concurrent and non-concurrent controls. For a given experimental arm, non-concurrent controls refer to data from patients allocated to the control arm before the arm enters the trial. While the use of non-concurrent controls in platform trials can increase the power of statistical tests, it comes with the risk of bias if time trends are present.

In this talk we review recently proposed frequentist and Bayesian procedures to incorporate non-concurrent controls that aim to adjust for potential time trends. We assess the procedures in a wide range of scenarios, varying the strength and pattern of time trends as well as the timings when experimental arms enter or leave the platform in a simulation study and compare the type 1 error rates and power to trials only using concurrent controls.

Bofill Roig, M., Krotka, P., Burman, C.F., Glimm, E., Gold, S.M., Hees, K., Jacko, P., Koenig, F., Magirr, D., Mesenbrink, P., Viele, K., Posch M. On model-based time trend adjustments in platform trials with non-concurrent controls. BMC medical research methodology, 22(1), 1-16, (2022).

Rainer Puhr:

BATS - The Bayesian Adaptive Trial Simulator

In clinical trials with time-to-event endpoints, adoption of Bayesian adaptive designs has frequently faced challenges due to the lack of readily available software and the prohibitive computational demands of Markov Chain Monte Carlo (MCMC) often employed to calculate the posterior distributions. The Bayesian Adaptive Trial Simulator (BATS) is a modular, highly-customisable R package that simulates Bayesian adaptive multi-arm multi-stage (MAMS) trials with adaptations on parameter posterior probabilities and evaluates frequentist operating characteristics. It makes use of integrated nested Laplace approximation (INLA) and its efficient implementation in R to perform approximate Bayesian inference in latent Gaussian models. Here we present a major extension for time-to-event data which provides a flexible, modular structure for the fast simulation of such designs. We demonstrate that BATS is an effective tool to study the operating characteristics of designs with time-to-event endpoints and commonly applied adaptations.