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Borrowing Strength or Buying Trouble? Using External Data in Regulatory Context

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Simon Wandel
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Simon Wandel holds a Master in Statistics and a PhD in Medical Statistics/Epidemiology, both from University of Bern. Since joining Novartis in 2010, he has worked in several disease areas both in early and late phase development. Currently, he is a Global Group Head in Advanced Quantitative Sciences in the Cardio-Renal-Metabolic Development Unit at Novartis. Simon has a broad interest in statistics (with a slight bias towards Bayesian approaches) and is particularly interested in bringing novel statistical concepts to live in clinical trials.

Juan Jose Abellan
Please provide a brief biography for the Presenting author(s)
Dr Juanjo Abellan is a senior specialist in biostatistics and real-world evidence at EMA. His interests include methodological aspects underpinning the generation of clinical evidence on the efficacy, effectiveness and safety of medicines. Prior to joining the EMA, he worked as a methodologist in the pharmaceutical industry for 10 years, and before then he worked as a statistician in various roles in Academia and Public Offices.

Franz König
Please provide a brief biography for the Presenting author(s)
Franz König is Associate Professor at the Institute of Medical Statistics at the Medical University of Vienna, Austria, where is head of the working group on adaptive designs. He is also member of the ethics committee in Vienna. From 2008 till 2010 he was seconded to the European Medicines Agency (London, UK) as statistical expert in the Unit Human Medicines Development and Evaluation. His main research interests are multiple testing, adaptive designs and interim analyses, data safety monitoring boards (DSMB) and master protocols focusing on platform trials. For example he was involved in the EU FP7- funded research project IDEAL, co-WP lead in the IMI project EU-Pearl on platform trials; and the ITN network IDEAS on early drug development studies. Currently is part of the European projects Share CTD, Invents and RealiseD.

Florian Klinglmueller
Please provide a brief biography for the Presenting author(s)
Florian Klinglmueller leads the Expert Group Biostatistics at the Austrian Agency for Health and Food Safety. He is a member of EMA’s Methodology Working Party, Big Data Steering Group and Emergency Task Force. Florian holds a PhD in Technical Mathematics and before joining the regulatory agency has spent several years in academic research focusing on topics related to clinical trial design, statistical computing and bioinformatics.

Single topic, multi-speaker session, Workshop or Single presentation submission

A single topic, mutli-speaker session/workshop

Single topic session or workshop abstracts

In this session, we will discuss the evolving landscape of hybrid clinical trial designs, which have attracted a lot of attention in recent years. Different types and aspects of hybrid clinical trial designs will be presented highlighting both the benefits but also the challenges when incorporating external data. How to ensure regulatory compliance if the hybrid trial is embedded in a drug development program and should provide pivotal evidence for regulatory decision making? The session aims to provide a comprehensive exploration of these aspects, featuring perspectives from regulators, industry, and academia.

Presentation 1 - Simon Wandel, Novartis
Thinking beyond the norm: how to (fairly) evaluate Bayesian Dynamic Borrowing designs

Bayesian Dynamic Borrowing (BDB) has become a topic of high relevance in clinical trials. While initial applications of BDB were mainly in early phases of drug development and/or rare diseases, recent work has focused on its general applicability in phase III studies. Multiple ongoing efforts by regulatory agencies (e.g., FDA, EMA, CDE) and cross-industry groups (e.g., PSI/EFPSI Special Interest Group “Historical Data”, ASA Biopharm Bayesian Scientific Working Group (BSWG)) further substantiate this. As part of these efforts, it has been recognized that classical metrics, such as Frequentist type I error and power, are insufficient to adequately quantify the possible benefits and risks associated with BDB designs. Alternative metrics and a more general framework are thus necessary to allow for a transparent, and somewhat harmonized, assessment of BDB designs. In this talk, I will discuss recent work from members of the PSI/EFSPI SIG “Historical Data” in the context of an ongoing effort for EMA qualification of BDB. I will also share insights from my own experience and shed light on a common misperception around Bayesian statistics, regarding inference vs. decision making.

Presentation 2 - Juan Jose Abellan, European Medicines Agency (EMA)
Another form of hybrid trial designs with external information: extrapolation in paediatrics

Medicine development in paediatric populations is challenging. Traditional clinical trial designs may not be feasible in these patient populations. In situations where the assessment of the extrapolation concept concludes that partial extrapolation of efficacy from adults is acceptable to generate evidence of efficacy in paediatrics, the corresponding paediatric investigation plan should include details on how extrapolation will be implemented. In this presentation, we discuss opportunities and challenges of paediatric trial designs intending to use results from adults for statistical inference of paediatric data, with a focus on methodological aspects of regulatory interest concerning both estimand and estimation.

Presentation 3 - Franz König, Medical University of Vienna
Echo of the Past: The Pre-specification Challenge in Hybrid RCTs

Hybrid Control RCTs augment data from randomized controlled trials with external controls, including historical or concurrent control data. A wide range of frequentist and Bayesian methods have been proposed to adjust for potential confounding. While these methods cannot guarantee strict type 1 error rate control, they can mitigate biases if the external controls differ systematically from the data in the RCT. A problem that received less attention so far, is the issue of pre-specification of the analysis. The selection of external controls involves many design decisions, as the choice of the data source, sample size, the inclusion and exclusion criteria, and the statistical methods used to include the external controls in the analysis. The validity of statistical inference depends on the assumption that these choices are made independently of the data. However, if historical data are used as external controls, often some information on this data may be (publicly) available at the time when a hybrid RCT trial is planned. This may be include aggregated outcome data in certain populations and subgroups or even data on an individual subject level. If this information is used in the planning of a hybrid trial, additional bias maybe introduced. The

problem of pre-specification may also arise if concurrent external controls are used. If, e.g., historic data are available for specific sites which is predictive for future outcomes and sites are chosen based on this data, a bias may be introduced.

Because a pre-specification of hybrid RCTs, independent of the external control data used may not be feasible, proper documentation of all design decisions and the information that was available at the time these decsions were made is required to mitigate the potential to introduce additional biases in the analysis of hybrid RCTs. Still hybrid RCTs might provide more robust evidence than single armed or underpowered standalone RCTs.

Presentation 4 - Florian Klinglmüller, Austrian Agency for Health and Food Safety
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.

References:

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