ASA NJ Chapter Webinar Series:

Getting the question right: Applying the Estimand and Target Trial Frameworks with External Controls

Dec 2, 2022, 10:00 am-12:20 pm (EST) 16:00-18:20 pm (CET)

Jointly by

New Jersey Chapter of the American Statistical Association

Oncology Estimand Working Group of ASA BIOP & PSI/EFSPI

WebEx link:
https://rutgers.webex.com/weblink/register/rc1de38e6142abe09e74e36b9c8533f40

(Note: please click the link above to register. Registration is free and brief. You will receive the calendar invite via email.)

Description

The use of the estimand framework for clinical trial protocols has gained increasing popularity since its introduction in the ICH E9 addendum. The framework facilitates the discussion about the trial objectives and helps to align the clinical research question with the analysis. In this webinar we will discuss the value of applying the estimand and target trial frameworks with external controls in drug development. Two case studies will illustrate how the framework can support multidisciplinary discussions and facilitate the dialogue with regulators in a transparent and structured way. Furthermore, the connection of the estimand framework with the target trial framework which has been used in epidemiology to ensure that non-randomized comparisons address the causal question interest will be highlighted. Regulatory and payer perspectives on the use of real-world data and the opportunities to overcome some of historical challenges by using these frameworks will be discussed. The webinar will include speakers from the industry, academia, regulatory and reimbursement bodies and target a broad statistical and non-statistical audience with an interest in real-world data.

Agenda

10:00-10:05	**Introduction** Brief overview of ASA NJ Chapter (Jing Gong, BMS) and Oncology Estimand Working Group of ASA BIOP & PSI/EPSPI (Evgeny Degtyarev, Novartis)
10:05-10:25	**External control arms in oncology: current use and future directions?** Speaker: Pallavi Mishra-Kalyani (FDA)
10:25-10:55	**Introduction to the ICH E9(R1) estimand and target trial emulation frameworks, and their role in the design and analysis of RWE studies** Speakers: Xabier Garcia de Albeniz Martinez (RTI Health Solutions) & Lisa Hampson (Novartis)
10:55-11:15	**Combining the target trial and estimand frameworks to define the causal estimand: an application using real-world data to contextualize a single-arm trial** Speaker: Jufen Chu (Novartis)

11:15-11:35	**Applying the Estimand and Target Trial frameworks to external control analyses using observational data: a case study in the solid tumor setting** Speaker: Letizia Polito (Roche)
11:35-11:50	**Benefits of target trial and estimand frameworks in real-world evidence of treatment effects for supporting health technology assessment** Speaker: Stephen Duffield (NICE)
11:50-12:20	**Panel Discussion and Q&A** Panelists: Andrew Thomson (EMA) and all presenters Moderator: Evgeny Degtyarev (Novartis)
12:20	**Closing**

Abstracts

Title: Introduction to the ICH E9(R1) estimand and target trial emulation frameworks, and their role in the design and analysis of RWE studies

Speakers: Xabier Garcia de Albeniz Martinez (RTI Health Solutions) & Lisa Hampson (Novartis)

Abstract: Central questions for drug development, licensing and reimbursement are to establish the existence, and to estimate the magnitude, of causal treatment effects, both in terms of efficacy and of safety. Estimating such effects requires a solid framework that begins by formalizing the question of interest by specifying: the patient population of clinical interest; the treatment strategies under study; the variable of interest, including the definition of time zero and the timing of key measurements; as well as the summary measure that will provide the basis for treatment comparisons. Strategies for handling intercurrent events may be reflected in these attributes; for example, treatment strategies should be composed by specific treatments, events that can affect such treatments and decision rules to apply when such events happen. Any remaining intercurrent events not reflected in these four attributes should also be detailed. Two frameworks have been developed in the context of clinical studies which do or do not randomize patients at baseline. This talk will introduce them, discuss their similarities, and reflect on how they might be deployed in combination to define estimands for RWE studies.

Title: **Combining the target trial and estimand frameworks to define the causal estimand: an application using real-world data to contextualize a single-arm trial**

Speaker: Jufen Chu (Novartis)

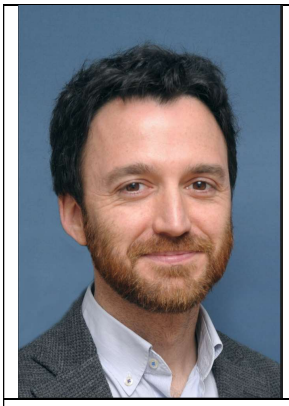
Abstract: Single-arm trials (SATs) may be used to support regulatory submissions in settings where there is a high unmet medical need and highly promising early efficacy data undermine the equipoise needed for randomization. In this context, patient-level real-world data (RWD) may be used to create an external control arm (ECA) to contextualize the SAT results. In this talk, we will show a case-study of a pivotal SAT of a novel CAR-T therapy for heavily pre-treated patients with follicular lymphoma to illustrate how a combination of the target trial and the ICH E9(R1) estimand frameworks can be used to define the target estimand and avoid common methodological pitfalls related to the design of the ECA and comparisons with the SAT. We also propose an approach to address the challenge of how to define an appropriate time zero for external controls who meet the SAT inclusion/exclusion criteria at several timepoints. Use of the target trial and estimand frameworks facilitates discussions amongst internal and external stakeholders, as well as an early assessment of the adequacy of the available RWD.

Title: Applying the Estimand and Target Trial frameworks to external control analyses using observational data: a case study in the solid tumor setting

Authors: Letizia Polito (Roche, presenter), Qixing Liang (Flatiron), Navdeep Pal (Genentech), Philani Mpofu (Flatiron) , Ahmed Sawas (Flatiron), Olivier Humblet (Flatiron), Kaspar Rufibach (Roche) , Dominik Heinzmann (Novo Nordisk)

Abstract: In causal inference, the correct formulation of the scientific question of interest is a crucial step. Here we apply the estimand framework to a comparison of the outcomes of patient-level clinical trials and observational data to help structure the clinical question. In addition, we complement the estimand framework with the target trial framework to address specific issues in defining the estimand attributes using observational data and discuss synergies and differences of the two frameworks. Whereas the estimand framework proves useful to address the challenge that in clinical trials and routine clinical practice patients may switch to subsequent systemic therapies after the initially assigned systematic treatment, the target trial framework supports addressing challenges around baseline confounding and the index date. We apply the combined framework to compare long-term outcomes of a pooled set of three previously reported randomized phase 3 trials studying patients with metastatic non-small cell lung cancer receiving front-line chemotherapy (randomized clinical trial cohort) and similar patients treated with front-line chemotherapy as part of routine clinical care (observational comparative cohort). We illustrate the process to define the estimand attributes and select the estimator to estimate the estimand of interest while accounting for key baseline confounders, index date, and receipt of subsequent therapies. The proposed combined framework provides more clarity on the causal contrast of interest and the estimator to adopt and thus facilitates design and interpretation of the analyses.

Bibliography



Xabier García de Albéniz, MD, ScM, PhD, is Director of Epidemiology at RTI Health Solutions. He has a background in oncology, epidemiology, and biostatistics. Dr. García de Albéniz has worked for several years within the Program on Causal Inference, Department of Epidemiology at the Harvard T.H. Chan School of Public Health, where he maintains an affiliation as collaborator of the CAUSALab. He currently collaborates on several academic research projects in the field of cancer and COVID-19 prophylaxis. Dr. García de Albéniz provides oncology and methodologic expertise to RTI-HS's Epidemiology group.

Jufen Chu is an associate director at Novartis/East Hanover site in New Jersey. She began her working career by joining Novartis in 2016. Since then, she has been working as trial statistician in many phase 1/b through phase 3 studies for the development of CAR-T therapy in different indications including diffuse large B-cell lymphoma and multiple myeloma. She was also leading the RWE work for the filling of Kymriah in follicular lymphoma indication. Ms. Chu received her PhD in Statistics from the University of Texas at Dallas in 2016.

Evgeny Degtyarev is Global Program Biostatistics Head leading a team of quantitative scientists on CAR-T program in hematology at Novartis. Since joining Novartis in 2013 he has supported several oncology programs with targeted and immunotherapies in different stages of development. He has co-founded and co-leads the industry working group “Estimands in oncology” in Feb 2018 which has been later granted the status of EFSPI/PSI Special Interest Group and ASA Biopharmaceutical Section Scientific Working Group **(www.oncoestimand.org).**

Dr Stephen Duffield is a senior Analyst at NICE Methods and Standards. Stephen’s role involves the continuing development of NICE’s real-world evidence (RWE) framework. collaboration on RWE demonstration projects, and helping to transform NICE’s use of real-world data across guidance products. Stephen is also involved with upskilling individuals within and externally to the organisation, contributing to training workshops and technical forums. Stephen has a degree in medicine and a PhD in public health. Previously, he worked as a clinical doctor and a guideline developer in NICE Centre for Guidelines

	**Lisa Hampson** is based in the Advanced Methodology & Data Science group at Novartis (in Basel, Switzerland), where her role is to support the development and implementation of innovative statistical methods. Prior to joining the pharmaceutical industry in 2016, Lisa was a Lecturer in Statistics at Lancaster University in the UK and held a UK Medical Research Council (MRC) Career Development Award in Biostatistics. Her research interests are in group sequential and adaptive clinical trials, Bayesian approaches for quantitative decision making, and the use of real-world evidence in pharmaceutical development.
	**Letizia Polito** is a Principal Data Scientist in Roche. She has strong scientific and technical expertise in observational research. Co-authors of more than 40 peer-reviewed manuscripts, she conducted research in different disease area, from Neuroscience, to infective diseases and finally in Oncology. In Roche, Letizia is working with real world data to generate impactful evidence and insights on molecules/medicines to advance scientific and medical knowledge to allow patients to get access to the personalized healthcare they need. In her day-to-day work, she cares to apply the most advanced epidemiological methodology and to highlight data quality limitations and solutions. Letizia graduated with a PhD in molecular epidemiology (Open University, UK) and she worked in a no-profit institution in Italy analyzing the relationship between molecular changes in the elderly and the etiology of age-related diseases of the brain in a longitudinal population-based study/human brain bank (Invece.Ab Study). After that and prior to her current role in Roche, Letizia worked in Glaxo Smith Klein as Sr. Biostatistician conducting observational studies involving primary data collection and secondary data use to address vaccine effectiveness and safety.
	**Andrew Thomson** is a statistician with over 15 years of experience in the regulatory system. He is currently at the EMA, in the Taskforce dedicated to Data, Analytics and Methodology. . Prior to joining the EMA in 2014, he spent 7 years at the UK Regulator, the MHRA, initially as a Statistical Assessor, and subsequently as Head of Epidemiology