Basel Biometrics Section webinar
"Basel", 7th September 2020

RCTs meeting causal inference: principal stratum strategy and beyond
Date: Monday, 7th September 2020, 14:00-17:00
Webinar: dial-in details will be communicated to registered participants

Noticing an emerging disconnect between clinical trial objectives and treatment effects actually estimated from them, the ICH E9 estimand addendum sought to define a framework which facilitates the alignment. Following the realisation that baseline randomisation may be insufficient to guarantee unbiased estimation of the "target" intervention effect, one aspect that has emerged quite naturally in the addendum is the need for analytical methods traditionally used for causal inference in non-interventional studies. However, the addendum does not explicitly mention the word causal.

The primary goal of this BBS webinar is to bring together the perspective from both causal inference researchers and clinical trial methodologists to discuss where methods developed in the causal inference literature can (or already did) support design and interpretation of clinical trials in pharmaceutical drug development. Questions that will be addressed include:

1) How do causal inference researchers see the ICH E9 addendum?
2) How does the estimands framework as put forward in the addendum relate to the target trial framework? Is it a convergence to a common ground from the "opposite" ends of observational and interventional worlds?
3) What are specific examples where causal inference methods can support design, analysis, or interpretation of drug trials?

The event will feature talks from statisticians in industry, academia, and regulatory agencies.

This is the second in a series of events dedicated to estimands for specific methods and therapeutic areas. Another webinar on estimands in neuroscience is currently planned.

The organizing committee of this event are Björn Bornkamp (Novartis), Giusi Moffa (University of Basel), and Kaspar Rufibach (Roche). The event is supported by the *European special interest group "Estimands in oncology", sponsored by PSI and EFSPI*, which is also an ASA scientific working group: http://www.oncoestimand.org.

If you'd like to attend please fill out the registration form. After registration you will receive a calendar invite with a webex link.

Attendees are invited to ask questions via the chat function in webex. These questions will either be commented on during the event or answered in writing an posted online, as for the first BBS estimand webinar.

Slides and recordings of some of the talks will be made available after the event on the BBS webpage, both pending speaker approval.

The webinar is free of charge.

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Program (find abstracts below):

14:00 – 14:10 **Kaspar Rufibach (member of BBS board and co-lead industry working group "estimands in oncology"**)
Welcome and scene setting

14:10 – 14:35 **Vanessa Didelez (Keynote speaker, Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen)**
Time-Varying Treatments in Observational Studies: Lessons for Clinical Trial

14:35 – 14:50 **Jack Bowden (University of Exeter)**
Connecting Instrumental Variable methods for causal inference to the Estimand Framework

14:50 – 15:05 **Kelly van Lancker (Ghent University)**
Efficient, doubly robust estimation of the effect of dose switching for switchers in a randomised clinical trial

15:05 – 15:15 **Break**

15:15 – 15:30 **Björn Bornkamp (Novartis)**
Principal Stratum Strategy: Potential Role in Drug Development

15:30 – 15:45 **Dominik Heinzmann (Roche)**
Principal stratum strategy to investigate anti-drug antibody impact on cancer immunotherapy outcome

15:45 – 16:00 **Aiesha Zia (Novartis)**
Exploring estimation approaches for principal stratum estimands in Phase III randomized trials in CAR-T anti-cancer therapy

16:00 – 16:10 **Break**

16:10 – 16:25 **Fabrizia Mealli (University of Florence)**
The ICH E9 addendum from an academic causal inference perspective and feedback on the previous talks

16:25 – 16:40 **Andrew Thomson (EMA)**
Regulatory feedback on the previous talks

16:40 – 16:55 **All speakers**
Comments on talks

16:55 – 17:00 **Giusi Moffa (member of BBS board)**
Next webinars and closure

We look forward to your participation!

Time-Varying Treatments in Observational Studies: Lessons for Clinical Trials

Vanessa Didelez

The field of causal inference deals with approaches for investigating the effects of (possibly hypothetical) interventions from observational data or imperfect trials. Logically, the first step of such an investigation is to define the target of inference, aka *causal estimand*. In this presentation, I will focus on the fact that in biomedical and epidemiological research most treatments or exposures are time-varying. Hence relevant target interventions will often need to be time-varying, too. This also applies to many RCTs, in particular when faced with intercurrent events, and essentially this is where the ICH E9 estimands addendum comes into play. I will give an overview of and discuss the ensuing issues, as well as ways to address them.

It is relatively easy to decide on a target of inference for a point-treatment/exposure, e.g. as a simple contrast like the average causal effect or the causal risk ratio, with further refinements to subgroup effects or comparison of survival curves. In case of time-varying treatments/exposures, specifying the target of inference is typically more challenging. Even if we simply wished to compare hypothetical interventions like, say, "always-treat" versus "never-treat", the fact that over time patients will not comply with these two options, possibly for good reasons, must be taken into account. So, while ideally, the choice of target of inference should be dictated by the research question or the decision problem at hand, we may often wish to allow for what is actually feasible in practice. The translation of the research question into a target of inference, or estimand, is a key issue, and should be an explicit part of any investigation (experimental or observational).

I will argue and illustrate that in many situations, including those addressed by the ICH E9 estimands addendum, it makes sense to consider dynamic or adaptive treatment strategies. This has long been recognized for epidemiological studies with time-varying exposures: see Robins (1986) and the many follow-up papers since, e.g. Dawid & Didelez (2010); also see, for instance, the monograph by Chakraborty & Moodie (2013) on optimal adaptive treatments. The renewed interest has been due to the debate around the ICH E9 addendum on estimands, which has been opened up the analysis of clinical trials to causal inference approaches originally aimed at observational data. On the observational studies side, interestingly, there is a recent push to use the "target trial" principles for analyzing observational data (Cain et al., 2016); these principles can be regarded as a systematic guide to formulating sensible causal estimands, and then carrying out the appropriate inference. Both developments appear like two sides of the same coin: an increasing awareness of the general need to be explicit about the target of inference, to design the study towards this aim, and to use suitable models and methods. This ensures a principled and coherent statistical analysis with practically useful results, where avoidable biases are avoided while plausibly minimizing biases that are not avoidable.

Cain et al. (2016). Using observational data to emulate a randomized trial of dynamic treatment-switching strategies: an application to antiretroviral therapy. International Journal of Epidemiology.

Chakraborty, Moodie (2013). Statistical Methods for Dynamic Treatment Regimes: Reinforcement Learning, Causal Inference and Personalized Medicine. Springer.

Dawid, Didelez (2010). Identifying the consequences of dynamic treatment strategies: A decision theoretic overview. Statistics Surveys.

Connecting Instrumental Variable methods for causal inference to the Estimand Framework

Jack Bowden

Instrumental Variables (IV) methods are gaining increasing prominence in the pharmaceutical arena in light of the recently published addendum on estimands and sensitivity analysis in clinical trials to the E9 guideline of the International Conference of Harmonization. The E9 addendum emphasises the need to account for post-randomization or 'intercurrent' events that act to distort the interpretation of a treatment effect estimate at a trial's conclusion. IV methods have been used extensively in epidemiology and academic clinical studies for 'causal inference', but less so in the pharmaceutical industry setting until now. We review the basic tools for causal inference, including graphical diagrams and potential outcomes, as well as several conceptual frameworks that an IV analysis can sit within. We discuss in detail how to map these approaches to the Principal Stratum and Hypothetical 'Estimand Strategies' proposed in the E9 addendum, and provide details of their implementation using standard regression models. Specific attention is given to discussing the assumptions each estimation strategy relies on in order to be consistent, the extent to which they can be empirically tested and sensitivity analyses in which specific assumptions can be relaxed. We apply the methods described to simulated data closely matching a recent pharmaceutical study to further motivate and clarify the ideas.

Efficient, doubly robust estimation of the effect of dose switching for switchers in a randomised clinical trial

Kelly Van Lancker

The interpretation of intention-to-treat analyses of randomised clinical trials is often hindered as a result of noncompliance and treatment switching. This has recently given rise to a vigorous research activity on the identification and estimation of so-called estimands. Motivated by an ongoing clinical trial conducted by Janssen in which a flexible dosing regimen is compared to placebo, we evaluate how switchers in the treatment arm (i.e., patients who were switched to the higher dose) would have fared had they been kept on the low dose in order to understand whether flexible dosing is potentially beneficial for them. Comparing these patients' responses with those of patients who stayed on the low dose does not likely entail a satisfactory evaluation because the latter patients are usually in a better health condition and the available information is too scarce to enable a reliable adjustment. In view of this, we will transport data from a fixed dosing trial that has been conducted concurrently on the same target, albeit not in an identical patient population. In particular, we will propose a doubly robust estimator, which relies on an outcome model and a propensity score model for the association between study and patient characteristics. The proposed estimator is easy to evaluate, asymptotically unbiased if either model is correctly specified and efficient (under the model defined by the restrictions on the propensity score) when both models are correctly specified. Monte Carlo simulations and application to a clinical trial conducted by Janssen demonstrated adequate performance.

Principal Stratum Strategy: Potential Role in Drug Development

Björn Bornkamp

The ICH E9 addendum outlines five strategies to acknowledge intercurrent events as part of the treatment effect/estimand of interest. The principal stratum strategy focuses on the subpopulation of patients where a specific intercurrent event does not (or does) occur. The principal stratum strategy is based on ideas from the causal inference literature and has not been commonly used in clinical trials so far. In this presentation we would like to review its concepts, discuss assumptions required for estimation as well as sensitivity analyses and go through examples, where we believe the strategy could be of use in drug development.

Principal stratum strategy to investigate anti-drug antibody impact on cancer immunotherapy outcome

Dominik Heinzmann

TBA

Exploring estimation approaches for principal stratum estimands in Phase III randomized trials in CAR-T anti-cancer therapy

Aiesha Zia

TBA