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Causal inference ESIG: introduction and applications of causal inference methodology in clinical trials.

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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 introduce the PSI/EFSPI Special Interest Group on causal inference. This newly formed ESIG is dedicated to the application of causal inference methodologies in the context of Randomized Controlled Trials (RCTs). We show in this session that there are opportunities to apply this methodology, within the regulatory framework outlined by the International Council for Harmonisation (ICH), including guidelines on estimands E9(R1) and other guidelines and directives from health authorities (e.g. the FDA guidelines on Baseline Covariate Adjustment). We intend to increase the uptake of methodologies that effectively address pertinent scientific questions, while accounting appropriately on how the data is collected and ascertaining if assumptions are satisfied. The session will start with introducing the special interest group and showcase two applications. The fourth talk will focus on the importance of sensitivity analyses. The session will be concluded with a discussion among the speakers addressing questions from the audience.

Introducing the Causal Inference Special Interest Group

In a first overview talk, **Sanne Roels (J&J)** and Kelly Van Lancker (Ghent Univeristy)**,** will introduce the causal inference ESIG, introduce and discuss 3 of the workings group's top prioritized topics to discuss and bridge to the other speakers. The first topic will be the importance of understanding the data generating mechanisms, the concept of counterfactuals and illustrate how these can be useful to better address the

scientific question of interest. Secondly the concept of a mediation perspective for estimation will be briefly introduced, and thirdly we discuss estimation strategies from a causal perspective and how these connect to other topics e.g. to common covariate adjustment strategies. This talk will set the stage for the 3 other speakers.

Mediation analysis in longitudinal randomised clinical trials with visit related outcomes

In a second talk, **Jesper Madsen (Novo Nordisk)**, Martin Linder (Novo Nordisk) and Stijn Vansteelandt (Ghent Univeristy) will talk on Causal mediation analysis. Questions around mode of action (MoA) of a drug have interest to scientific communities as well as regulatory authorities. In the absence of an already established MoA such questions may be enlightened by causal mediation analysis in clinical trials. We present a general framework that facilitates causal mediation analysis in a setting of a clinical trial where both the outcome of interest, one or more mediators and additional potential post baseline confounders are measured repeatedly at planned visits. The targeted estimands are path-specific effects implicitly defined from a causal diagram that includes all the longitudinally measured variables. The framework including estimation method is developed with inspiration from a similar approach for time-to-event outcomes. The novelty of our approach compared to many currently used methods is that it directly establishes MoA, takes the full amount of longitudinal data into account, and properly adjusts for sources of confounding. We motivate and illustrate the approach with examples from the STEP 2 clinical trial.

Implementation of the ICH E9 (R1) Addendum in Vaccine Efficacy Studies: The Hypothetical and Principal Stratum Strategies

In a 3rd talk, Silvia Noirjean, Daniele Bottigliengo, Elisa Cinconze, Ali Charkhi, Toufik Zahaf, Fan Li, AndreaCallegaro **Andrea Callegaro (GSK)** will discuss the application of the estimand framework in vaccine studies. Over the past decades, the primary interest in vaccine efficacy evaluation has mostly been on the effect observed in trial participants complying with the protocol requirements (per protocol analysis). The ICH E9 (R1) addendum provides a structured framework to formulate the clinical questions of interest and formalize them as estimands. In this presentation, the estimands framework is retrospectively implemented in a Human papillomavirus (HPV) phase 3 trial, where the vaccine efficacy was originally estimated on the per protocol set. We focus on two strategies for dealing with the presence of intercurrent events: the hypothetical and the principal stratum strategies. We address the interpretation of two estimands, their estimation as well as articulation of the underlying identifiability assumptions. Finally, we leverage the results of the HPV application to formulate general considerations regarding the implementation of the ICH E9 (R1) addendum in vaccine efficacy studies.

Making sense of sensitivity analyses

In the last talk, **Tim Morris (UCL)**, Kelly Van Lancker (Ghent University), will discuss the importance of addressing and understanding assumptions underlying causal inference methodology. The presentation will detail the importance by addressing identifiability

assumptions such as positivity, exchangeability, consistency, ignorability, cross-world assumptions and the implications for estimation and interpretation.