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Continuing the Estimand Journey – 3 important topics you don’t want to miss!

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Antonia Morga
Please provide a brief biography for the Presenting author(s)
Antonia Morga is the Senior Director, Global HEOR and HTA Strategy Lead at Astellas Pharma, where she drives strategies to navigate and influence the global health technology assessment (HTA) environment, and is responsible for evidence-generation plans for products in the Specialty Therapeutic Area space.

She serves as Vice-Chair of the European Federation of Pharmaceutical Industries and Associations (EFPIA) HTA Working Group, contributing to policy and methodological advancements in HTA across Europe. Antonia also co-leads the EFSPI Estimands Implementation Working Group’s sub-team, which focuses on incorporating the ICH E9(R1) Addendum on Estimands in HTA processes and real-world evidence studies.

James Bell
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James originally trained as a chemist, receiving his PhD from the University of Cambridge in 2009. Following a short spell in industry doing computational drug design, he completed his MSc in statistics at UCL in 2013. Starting at Boehringer Ingelheim, he spent three years as trial statistician before joining the statistical methodology group. James now works as a consultant methodology statistician for the CRO Elderbrook Solutions GmbH, providing services to a major pharmaceutical company. James is an active member of cross-industry WGs on his two main areas of research, estimands and missing data handling, and is the chair of the estimation subteam of the EIWG. Other areas of particular interest include event prediction and the process of how trials are designed.

Gabriele Bleckert
Please provide a brief biography for the Presenting author(s)
Dr. Gabriele Bleckert is currently working as an Expert Clinical Statistics (Late Phase) at Staburo GmbH, Munich, specializing in providing statistical services to the healthcare industry. She earned her Ph.D. in Mathematics from the University of Munich & Bremen, Germany, and holds a Master in Biostatistics from the University of Heidelberg, Germany. Over the past 10 years, her statistical contributions focussed on late phase clinical drug development mainly in the indication of oncology and T2DM/chronic weight management. Dr. Bleckert is actively involved in the Estimand Implementation Working Group to incorporate estimands in all relevant facets of a clinical trial.

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

A single topic, mutli-speaker session/workshop

Single presentation or poster submission

Poster submission

Single topic session or workshop abstracts

This session is sponsored by the Estimand Implementation Working Group (EIWG) and includes presentations on these 3 important topics:

1. Reflections on ICH E9(R1) in Health Technology Assessments and the new EU Joint Clinical Assessment
2. Estimands in disclosure and the collaborations between EIWG members with NIH to develop best practices in reporting estimands and clinical trial results on ClinicalTrials.gov
3. Estimands which are using composite strategies to address an intercurrent event(s) involving a continuous endpoint and challenges for assigning 'bad outcomes'

1. Reflections on ICH E9(R1) Addendum in the Context of the EU's Joint Clinical Assessments

Background: The implementation of the estimands framework (ICH E9(R1) Addendum) has enhanced clarity in regulatory decision-making around treatment effect estimation. There is growing interest in how the ICH E9(R1) Addendum principles have been incorporated into the methodological guidance documents for the EU's Joint Clinical Assessment (JCA). Ensuring that the estimand framework is effectively applied in the Health Technology Assessment (HTA) context is crucial, particularly in addressing relevant clinical questions and informing decision-making. It is essential to explore how estimand attributes align with PICO (Population, Intervention, Comparator, Outcome) within the JCA context to ensure evidence generation strategies meet both regulatory and HTA requirements.

Objective and Methods: We evaluate the integration of the ICH E9(R1) Addendum into EU HTA methodological guidance documents, focusing on PICO alignment with estimands as well as on how estimands capture questions of interest in the JCA. Additionally, we explore whether HTA Agencies and Regulatory Authorities are now speaking a common language in their application of estimands, highlighting overlaps between PICO and estimand attributes. Our review of relevant methodological guidance documents assesses the extent to which the ICH E9(R1) principles have been incorporated into HTA methods, identifying both progress and areas needing further clarification, especially in aligning estimand attributes with the PICO framework.

Results and Conclusions: While estimands are increasingly recognized within HTA methodological guidance documents, significant gaps remain in fully integrating them. The lack of alignment between PICO and estimand attributes can lead to inconsistencies in how evidence is generated and interpreted for HTA purposes, making it challenging to assess the relevance and robustness of treatment effects for decision-makers. Clearer guidance is needed to ensure consistent application of estimands, thereby enhancing the quality and relevance of evidence for both regulatory and HTA evaluations.

2. Estimand disclosure on ClinicalTrials.gov

With estimands being adopted by both the FDA and EMA they are becoming a mainstay in clinical trial design, conduct, analysis, and interpretation. Since the introduction of the (ICH E9 R1) Addendum on estimands, sponsors have begun adding the description of estimands and the numerical results of the estimation(s) targeting the estimand(s) to the records of their clinical trials on ClinicalTrials.gov - with mixed outcome. As there are no dedicated fields in the study record of ClinicalTrials.gov for estimands, sponsors add estimand information in varying detail and different places throughout the forms provided by ClinicalTrials.gov. These inconsistencies are confusing for the reader and go against the aim of introducing estimands, which is, to avoid misinterpretation of the reported treatment effect(s) and to clarify exactly which treatment effect(s) the trial is assessing.

In a collaboration with the ClinicalTrials.gov team at the National Institutes of Health (NIH) we have developed guidance on how to include your estimand description to the registration form of your trial on ClinicalTrials.gov and, upon completion of the trial, how to present the numerical results of the estimation(s) targeting the estimand(s) in the study results form. Following these recommendations will lead to more consistent and complete public disclosure of estimands, allowing sponsors to properly inform any stakeholder about the key scientific/clinical questions of their trial. In conclusion, a guidance on how to disclose an estimand will foster the use of the estimand framework in the scientific community.

3. Continuous Composite Endpoints: How Bad Is Too Bad?

Composite variable strategies for addressing intercurrent events (ICEs) such as death or treatment discontinuation are common in binary, time-to-event and recurrent event type endpoints, fitting into the concepts of recording whether and when a ‘bad outcome’ occurred. Common examples include PFS in oncology and the Major Adverse Cardiovascular Events (MACE) endpoints in cardiology. However, recently composite handling has also been requested by some regulators in settings where the outcome is continuous, such as Forced Vital Capacity (FVC).

For continuous outcomes it is unclear what ’bad outcome’ value to assign an ICE such as death or surgery; there may be no clinically plausible value to choose, or it may lie far from values expected in living patients. Although rank-based approaches have been suggested as a possible solution, typically the mean remains the summary measure of interest and consequently the exact value matters for both the definition of the clinical question of interest and its statistical properties.

In this talk, the Estimation Subteam of the Estimands Implementation Working Group will discuss the choice of ’bad outcome’ for continuous composite outcome value, presenting findings and recommendations. We will demonstrate the statistical impact of different choices of the death outcome value on variance using an example in a respiratory disease setting, showing how ‘zero outcome’ approaches can dramatically lower power. Finally, we discuss whether a mean of a continuous composite outcome is clinically meaningful, or whether it is better to change summary measure, or assess the outcomes separately but interpret collectively.