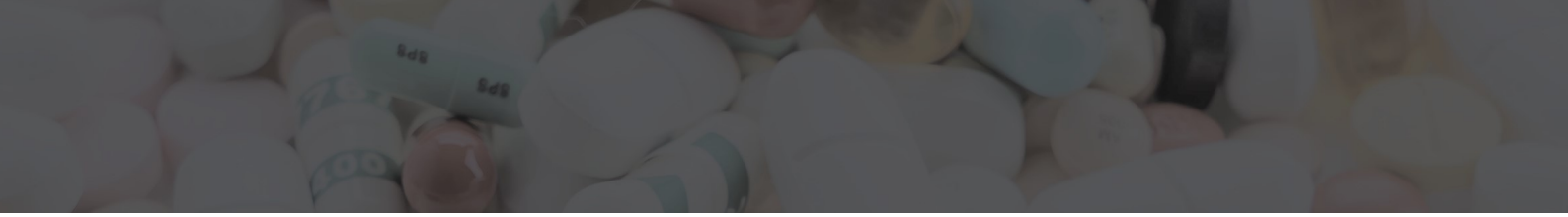


EFPIA / EFSPI ESTIMAND IMPLEMENTATION WORKING GROUP (EIWG)

efpia
European Federation of Pharmaceutical Industries and Associations

EFSPI
EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

"EIWG brings together statisticians and clinicians to support the estimand journey"

EIWG Scope & Setup

To provide a cross-industry forum to:

- Share Industry and Academic experiences of implementing the new estimand framework introduced in ICH E9(R1
- Discuss issues emerging through implementation
- Be champions and engage in scientific discussion about the value and benefits of the framework

With the aim to:

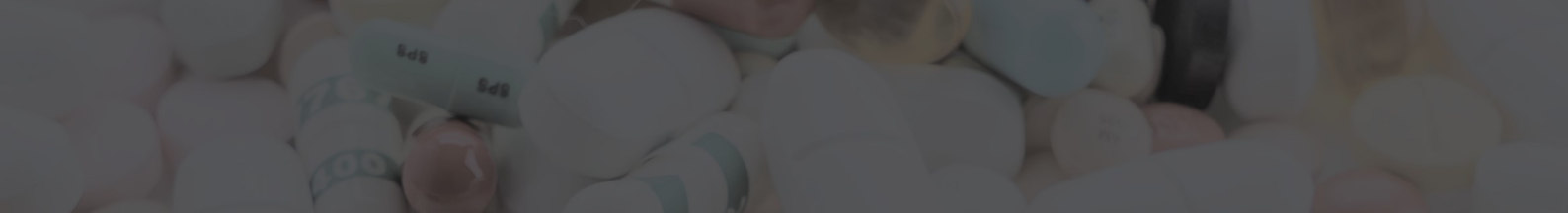
- Give feedback and recommendations for best practices
- Promote broad understanding and awareness of the framework within and outside of statistics
- Consolidate issues and topics for discussion with the ICH E9 Implementation Working Group

EIWG is setup to be diverse and inclusive when it comes to companies' representation. Currently 59 members represent 32 companies and institutions.

EIWG Structure & Topics

The EIWG is co-lead by Amel Besseghir, Chrissie Fletcher and Nanco Hefting. The working group is operating in seven sub-teams.

The most recent sub-team focuses on late phase and on the impact of estimands in Health Technology Assessment (HTA) and Real World Evidence (RWE).



EIWG Achievements 2022

Training sub-team

The training committee has continued to work on webinars for their training series 'EIWG Estimand Training Academy' targeting anyone working in clinical trials.
All trainings provided so far are freely available as 'Video-on-Demand'
Portal: https://psiweb.org/vod/Index/ or YouTube on the EFPIA channel

Estimation sub-team

Estimating the treatment-policy strategy with continuous data and incomplete post-IE follow-up is a relevant and under-researched issue. To address it, the group has assessed the performance of different estimators – based on either multiple imputation (MI) or mixed effect models (MMRM) – for simulated trials based on the HbA1c endpoint from the PIONEER1 study.
The properties of the estimators (bias and variance shown here) generally confirm the equivalence of MI and MMRM approaches (if the same assumptions are made) and the particular importance of collecting post-IE data. The complex trade-off between variance inflation and accuracy needs to be carefully evaluated further.

Early Phase & Other Studies sub-team

This sub-team was created as a forum for both statisticians (industry & academia) and pharmacokinetics as well as regulators to help bridge the gap in the estimands framework with regards other study types including early phase and clinical pharmacology where the purpose is not confirmatory efficacy. We presented a poster (Does the Estimand Framework Add Value to Clinical Pharmacology Trials?) at the PSI conference 2022. A manuscript is under preparation with focus on bioequivalence/ bioavailability studies and is planned to be published in a clinical pharmacology journal in 2023. The implementation of estimands in early phase studies (including dose finding and CRMs) are also being discussed within this workstream. We aim to share some of our work at the PSI conference in 2023.

Communications

In 2022 the homepage of the group was fully revised and summarizes all work of the EIWG.

Posters of the working group were presented at the 2022 PSI conference in Gothenburg and the 2022 Regulatory Industry workshop in Basel.

Estimands in non-inferiority trials

The ICH E9(R1) includes limited guidance in relation to non-inferiority (NI) trials. Current regulatory guidelines on NI trials predate the release of the addendum and the per protocol analysis set plays an important part in the EMA NI guidelines. In contrast, ICH E9(R1) questions the role of the per protocol set and this has led to confusion as regards to the applicability of the EMA Points to consider on switching between superiority and non-inferiority.
The sub-team is discussing which estimands can be considered relevant in an NI setting and how they fit into existing guidelines. The sub-team members are sharing recent regulatory feedback on NI trials, and we are discussing questions such as

- What is the underlying clinical question to be answered in an NI trial?
- Are two estimands with different strategies for intercurrent events required to reflect the spirit in the EMA Points to consider on switching between superiority and non-inferiority?
- Can protocol violations be handled as intercurrent events? Is there any remaining role for a Per Protocol analysis set?
- Can different estimands be used to show NI and superiority in the same trial (hierarchical set-up)?
- How does the estimand framework impact the choice of the NI margin?

The sub-team is planning to prepare a manuscript on these topics.

EIWG Puplications 2022

- A. Morga, NR. Latimer, M. Scott, N. Hawkins, M. Schlichting, J. Wang. Is Intention to Treat Still the Gold Standard or Should Health Technology Assessment Agencies Embrace a Broader Estimands Framework?: Insights and Perspectives From NICE and IQWiG on the ICH E9(R1) Addendum. Value Health. 2022 Sep 20:S1098-3015(22)02148-9. https://doi.org/10.1016/j.jval.2022.08.008
- H. Lynggaard, J. Bell, C. Lösch, A. Besseghir, K. Rantell, V. Schoder, V. Lanius. Principles and Recommendations for Incorporating Estimands into Clinical Study Protocol Templates. Trials (2022) https://doi.org/10.1186/s13063-022-06515-2
- C. Fletcher, N. Hefting, M. Wright, J. Bell, J. Anzures-Cabrera, D Wright, H. Lynggaard, A. Schueler. Marking 2-years of new thinking in clinical trials - the estimand journey. Ther Innov Regul Sci 56, 637–650 (2022). https://doi.org/10.1007/s43441-022-00402-3
- D. Wright, H. Lynggaard , S. Englert, V. Lanius, O. Keene. Why Estimands are Needed to Define Treatment Effects in Clinical Trials. Submitted