UPDATE - Estimand Implementation Working Group (EIWG)

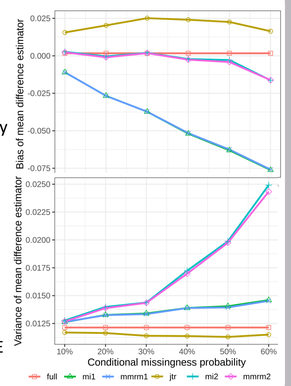
Training Subteam

- Our aim is to promote the use of the estimand framework through case studies.
- Up to now we have produced three webinars that are available in the PSI VoD library and in the EFPIA YouTube channel:
  - PIONEERing estimands in Clinical Research.
  - Estimands in Oncology – How and Why.
  - Estimands from trial planning to publication in medical journals: The ETHOS trial.
- Next webinar (TBC 2022): Impact of estimands – sharing our experience.

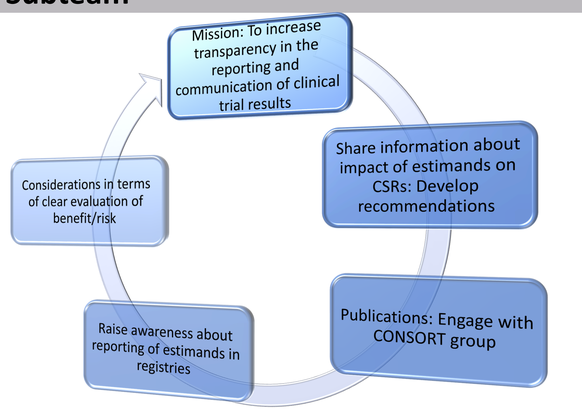
The Estimands Academy for Trial Teams
"Bringing estimands to *life* through real case studies"

Estimation Subteam

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 simulated trials based on the HbA1c endpoint from the PIONEER1 study in type 2 diabetes. This contains many patients discontinuing the assigned treatment and switching to rescue therapy. Trials have been simulated under varying parameters (including probability to continue follow-up post-IE and post-IE trajectories) to test the performance of different estimators. The estimators – based on either multiple imputation (MI) or mixed effect models (MMRM) – made different assumptions on the post-IE trajectories: Ignore whether an IE occurred (MI1 and MMRM1); immediate, but undefined, off-treatment impact upon discontinuation (MI2 and MMRM2) or immediate loss of active treatment effects upon discontinuation (jump to reference, J2R). 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.



Reporting Subteam



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

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**

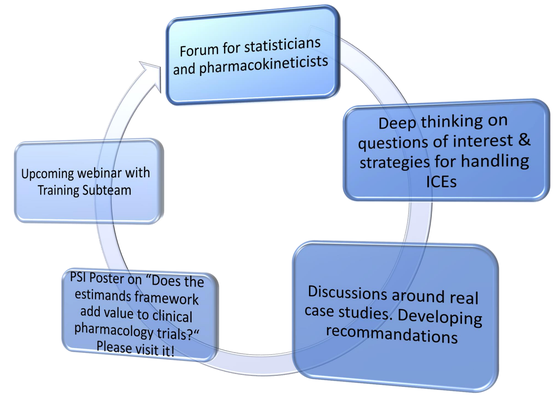
With the aim to:

- **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**

Currently operates in 6 subteams (left and right columns)

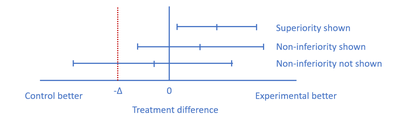
https://www.efspi.org/EFSPI/Working_Groups/EFSPI_EFPIA_EIWG.aspx

Early Phase and Clinical Pharmacology Subteam



Non-Inferiority Subteam

Regulatory guidelines, [1,2] specify how non-inferiority (NI) should be established based on both the intention-to-treat (ITT)-analysis set and the per protocol (PP) set [1], or ITT only [2]. The introduction of ICH E9(R1) [3] challenges these requirements. The sub-team shares case studies and regulatory feedback, discusses which estimands would be considered relevant in an NI setting and how they fit into existing guidelines.



References:

1. Points to consider on switching between superiority and non-inferiority. CPMP/EWP/482/99.
2. Non-inferiority clinical trials to establish effectiveness. Guidance for Industry, FDA 2016.
3. ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (2019)

Specifically, the sub-team discusses

- What is the underlying question to be answered in a NI trial?
- Are two estimands required to reflect the spirit in [1]?
- Does it makes sense to use the treatment policy strategy to handle treatment discontinuation and use of additional medication?
- Is the treatment effect to be estimated in adherers?
- Which implications do estimands have on the choice and justification of the NI margin?
- Can different estimands be used to show NI and superiority in the same trial (hierarchical set-up)?

The sub-team plans to submit a paper on these and other considerations.

Communications Subteam

- Promote activities completed to date
- Advertise trainings freely available as 'Video-on-Demand' on the PSI portal and Youtube: https://psiweb.org/vod/Index/
- Partner with related groups
  - Special interest group "Estimands in oncology", sponsored by PSI and EFSPI and ASA scientific working group
  - PhUSE
  - TransCelerate
- Build a 'One-stop-shop' for Estimand related training and educational content (planned for end of 2022)

The EIWG consists of 59 members representing 30 companies and institutions.

Publications:

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.* Submitted

D. Wright, H. Lynggaard , S. Englert, V. Lanius, O. Keene. *Estimands and True Treatment Effects.* Submitted

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* (2022). doi: 10.1007/s43441-022-00402-3

O. N. Keene, D. Wright, A. Phillips, M. Wright. *Why ITT analysis is not always the answer for estimating treatment effects in clinical trials* (2021). doi: 10.1016/j.cct.2021.106494