Feedback from the EFSPI / EFPIA Estimand Implementation Working Group

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David Wright[1], Vivian Lanius[2] and Armin Schüler[3] on behalf of the EIWG

1 Head of Statistical Innovation, Early Biometrics and Statistical Innovation, Data Science and Artificial Intelligence, R&D, AstraZeneca, Cambridge UK.

2 Expert Statistician Thrombosis & Hematology, Statistics & Data Insights, R&D, Bayer AG.

3 Head of Biostatistics Oncology, Biostatistics, Epidemiology & Medical writing, Merck Healthcare KGaA.

EFPIA / EFSPI Estimand Implementation Working Group (EIWG)

EIWG brings together statisticians and clinicians to support the estimand journey

Acknowledgements

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EIWG Members

Institution	Member
AMGEN	Mary Elliott-Davey
AstraZeneca	David Wright
BAYER	Vivian Lanius
Boehringer Ingelheim	James Bell
CONSILIUM Salmonson & Hemmings	Rob Hemmings*
PT Stat Consulting	Paul Terrill
gsk	**Chrissie Fletcher⁺**
	Oliver Keene
	Jatin Patel (C)
	Millie Wang (C)

Institution	Member
IQVIA	Maria Efstathiou
LEO	Christian Pipper
Lilly	Pepa Polavieja
Lundbeck	**Nanco Hefting⁺** (C)
	Mette Josiassen
medac	Michael Tribanek
MERCK	Armin Schueler
MHRA	Khadija Rantell
mundipharma	Nick Manamley
NOVARTIS	Melanie Wright

Institution	Member
novo nordisk®	Helle Lynggaard
	Irina Matytsina (C)
	Rikke Mette Agesen (C)
Pfizer	Maria Dilleen
	Rod Junor (C)
PPD®	Sue McKendrick
	Nikolay Stoyanov
Roche	Judith Anzures-Cabrera
SERVIER	Estelle Lambert
ucb	Christian Loesch
	Katsumi Yoshida

⁺Co-Lead *Adhoc member C = Clinician

EIWG Charter – Purpose

- To provide a cross-industry forum to:
  - share Industry experiences of implementing the new estimand framework introduced in ICH E9(R1) and
  - engage in scientific discussion about the value and benefits of the framework

- With the aim to:
  - give feedback and recommendations for best practices
  - consolidate issues and topics for discussion with the ICH E9 Implementation Working Group
  - to raise awareness and promote the value of the framework across industry and beyond

Activities up-to now

Monthly Meetings including a full-day kick-off meeting

- Sharing of estimand implementation plans and current status at each company at the kick-off meeting
- Going through ICH E9(R1) line by line as a team to get a common understanding
  → top 5 priorities of the EIWG (pre-COVID-19):
  - Role of analysis sets
  - Incorporating the new framework into protocols and SAPs including impact to standards
  - Training materials
  - Common understanding of the guideline, and
  - Impact to programming.
- Impact of COVID-19 from an Estimands perspective
- Review of ICH M11 protocol template & best practices for incorporating estimands into protocols
- Alignment on training plan
- Alignment on engagement and advocacy plan

Activities up-to now

Communications

- PSI annual meeting: Session on Impact of COVID-19 to Estimands
- Feed information and experience on estimands into other cross-Pharma groups (for example Pharmaceutical Industry COVID-19 Biostatistics Working Group and TransCelerate).

What (benefits) do members take out of the EIWG?

- Motivation & Inspiration: interest in improving trial design and best practice to “future proof” clinical trials
- Networking: exposure to a broader network of involved clinicians and statisticians
- Learning & Understanding: reflection on ICH E9(R1) to achieve a greater & common understanding, appreciation of challenges, gaps, caveats and opportunities for practically implementing estimand framework thinking, highlighting areas where regulatory guidance would be helpful
- Sharing & Soundboard: opportunity to very openly share

on the implementation of estimands
across companies,
therapeutic areas, and functions
eventually helping to develop a consistent approach

- Ad-hoc benefit: discussion of the impact of COVID-19 using estimand framework
- Awareness & Influencing: learn about and contribute to

Ongoing/planned Activities

Activities to raise awareness and promote the value:

- Training through case studies
- Communication plan highlighting emerging news and trends relating to estimands

Activities to provide recommendations on best practices:

- Develop best practices to provide documentation in clinical trial protocols/SAPs
- Develop generic case studies to support implementation
- Outreach and collaboration with key stakeholder groups, *e.g.*, TransCelerate

Ongoing/Planned Activities - Training

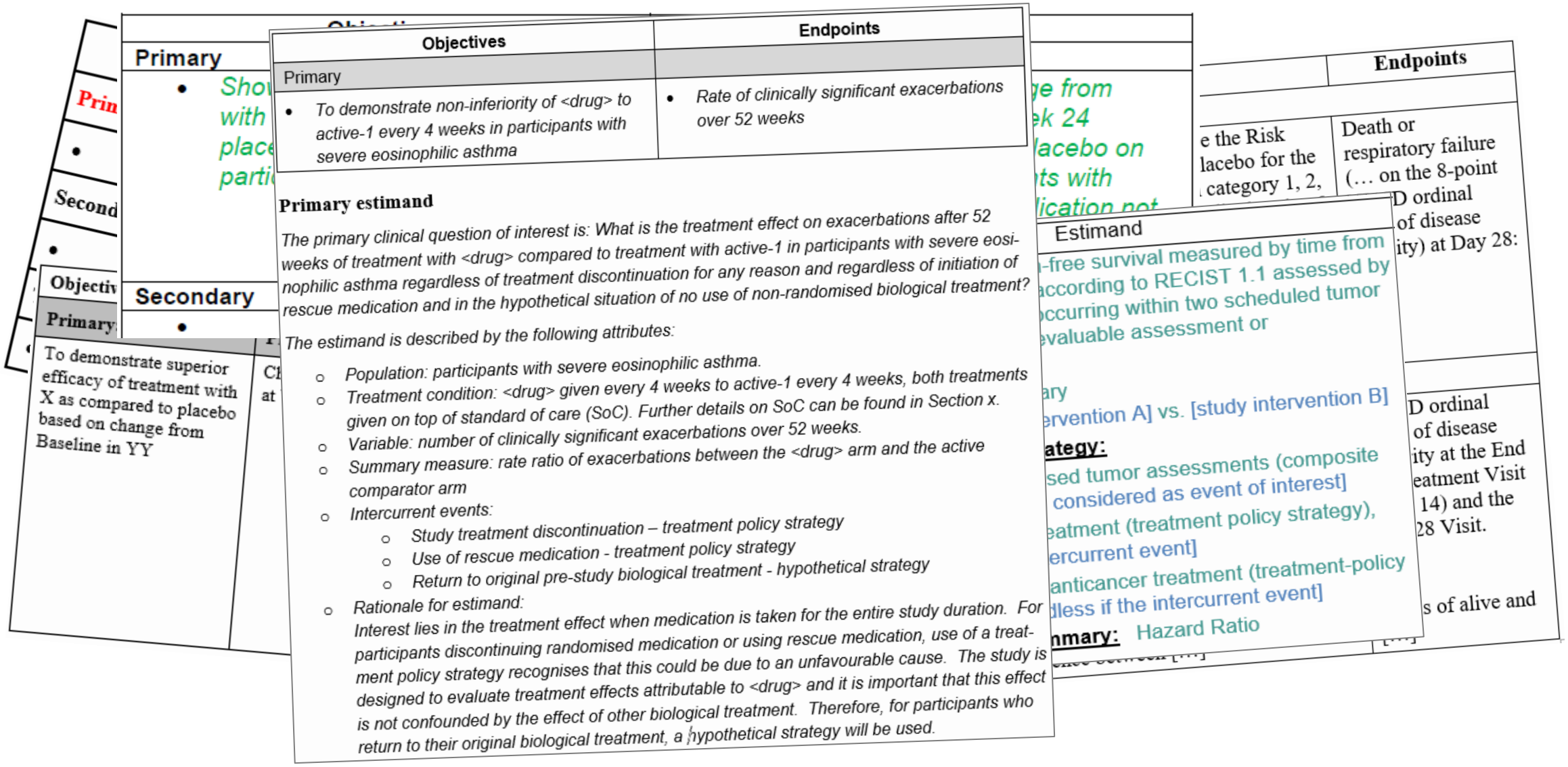
Training concept

- Introduce the value and benefits of the estimand framework through real life case study examples for which results are available in the public domain.
- The approach has been chosen as complementary to the existing training material available through the ICH website.
- Webinar format
- For each case study:
  - the background will be provided, intercurrent events of interest will be discussed
  - Will be used as a vehicle to highlight different aspects of interest to invoke some discussion/reflection

Target audience

- Cross functional audience: clinician, regulatory affairs, medical writers, statisticians, investigators working in pharmaceutical industry, public health or academia.
- As a second step, separate case study discussions focusing on aspects of interest to a statistical audience may be developed

Estimands in Study Protocols – a Patchwork Quilt at the Moment?



Objectives	Endpoints
Primary	
• To demonstrate non-inferiority of <drug> to active-1 every 4 weeks in participants with severe eosinophilic asthma	• Rate of clinically significant exacerbations over 52 weeks

Primary estimand

The primary clinical question of interest is: What is the treatment effect on exacerbations after 52 weeks of treatment with <drug> compared to treatment with active-1 in participants with severe eosinophilic asthma regardless of treatment discontinuation for any reason and regardless of initiation of rescue medication and in the hypothetical situation of no use of non-randomised biological treatment?

The estimand is described by the following attributes:

- *Population: participants with severe eosinophilic asthma.*
- *Treatment condition: <drug> given every 4 weeks to active-1 every 4 weeks, both treatments given on top of standard of care (SoC). Further details on SoC can be found in Section x.*
- *Variable: number of clinically significant exacerbations over 52 weeks.*
- *Summary measure: rate ratio of exacerbations between the <drug> arm and the active comparator arm*
- *Intercurrent events:*
  - *Study treatment discontinuation – treatment policy strategy*
  - *Use of rescue medication - treatment policy strategy*
  - *Return to original pre-study biological treatment - hypothetical strategy*
- *Rationale for estimand:*
  Interest lies in the treatment effect when medication is taken for the entire study duration. For participants discontinuing randomised medication or using rescue medication, use of a treatment policy strategy recognises that this could be due to an unfavourable cause. The study is designed to evaluate treatment effects attributable to <drug> and it is important that this effect is not confounded by the effect of other biological treatment. Therefore, for participants who return to their original biological treatment, a hypothetical strategy will be used.

Estimands in Study Protocols – a Patchwork Quilt at the Moment?

Different companies are using slightly different ways of expressing Estimands in protocol templates

Ongoing process on

- What level of detail is needed in §3 of the protocol on estimands?
- How to include Estimands into the Objectives/Endpoints Table in the Protocol?

One of the roles of the EIWG is to celebrate good practice here and make recommendations to cross Pharma groups such as TransCelerate to establish an appropriate standard way of incorporating Estimands into clinical trial protocols.

Principles for Incorporating Estimands into Clinical Trial Protocols

- **Estimand concept – required for all trials using the template?**
  - Encourage use of estimands!
    If optional, estimands concepts cannot be integral to the template structure → modularity
    - Note that many of the estimands elements are still relevant.
- **Role and level of detail for objectives**
  - Definition at low detail level ("To show efficacy")?
  - Definition at high detail level (detailed clinical objectives, i.e., estimand attributes jointly with desired goal/claim)?
- **Protocol structure**
  - Focus to shift from traditional structure around endpoints to estimands and/or objectives

– work in progress –

Communication & Advocacy Plan

- Regular updates on EIWG activities via EFSPI & EFPIA newsletters
- Information, news and articles of interest on EFPIA & EFSPI websites
- '1-year after ICH E9(R1)' publication (end 2020)
- Work with EFPIA to reach out to clinical researchers, regulatory affairs, investigators, patients
  - Understanding, awareness, training
- Work with ISPOR to reach out to HTA/payer stakeholders
- Collaborate with other societies and scientific debate, e.g., DIA, ASA
- Connect with ICMJE to incorporate estimands into publications
- Connect with CT.GOV to incorporate estimands into clinical trial registries
- Collaborate with TransCelerate and CPT/CSAP
- Collaborate with PhUSE on programming aspects
- Share experiences and feedback with ICH E9 WG

Summary

- Group is thriving with multiple different subteams working on Communication, Training and describing estimands in protocols and SAPs.
- Look out for first case study webinar later this year and more to come in 2021.
- If others are interested in joining the group please contact Chrissie Fletcher chrissie.a.fletcher@gsk.com

References and Additional Resources

- See papers in Therapeutic Innovation and Regulatory Science (2020):
  - Choosing Estimands in Clinical Trials: Putting the ICH E9(R1) Into Practice
  - Defining Efficacy Estimands in Clinical Trials: Examples Illustrating ICH E9(R1) Guidelines
  - Aligning estimators with estimands in clinical trials: Putting ICH E9(R1) guidelines into practice

- Statistical issues and recommendations for clinical trials conducted during the COVID-19 pandemic, Statistics in Biopharmaceutical Research (2020):
  https://www.tandfonline.com/doi/full/10.1080/19466315.2020.1779122

- See recent “Virtual” Issue of Pharmaceutical Statistics on Estimands:
  https://onlinelibrary.wiley.com/doi/toc/10.1002/(ISSN)1539-1612.estimands-virtual-issue

Thank you

Any Questions?