Implementation of the estimand framework in clinical study protocol templates

Helle Lynggaard,

Novo Nordisk A/S

29 April 2022

Disclaimer

- The presenter is employed by Novo Nordisk A/S, is a member of TransCelerate Clinical Content & Reuse (CC&R) track and the Estimand Implementation Working Group (EIWG). The views expressed by the presenter are not necessarily the views and practices of Novo Nordisk A/S, TransCelerate or all EIWG members

Acknowledgements

- For co-authoring of the “Principles and Recommendations for Incorporating Estimands into Clinical Study Protocol Templates”
  - James Bell, Elderbrook Solutions GmbH, UK
  - Amel Besseghir, UCB Pharma, Brussels, France
  - Vivian Lanius, Bayer, Germany
  - Christian Lösch, UCB Biosciences GmbH, Germany
  - Khadija Rantell, Medicines and Healthcare Products Regulatory Agency, UK
  - Volker Schoder, Metronomia Clinical Research GmbH, Germany

- Joined presentation at PSI 2021 with Pepa Polavieja, Lilly

EFPIA / EFSPI
Estimand Implementation Working Group (EIWG)

EIWG brings together statisticians and clinicians to support the estimand journey

EIWG members as of 4 April 2022

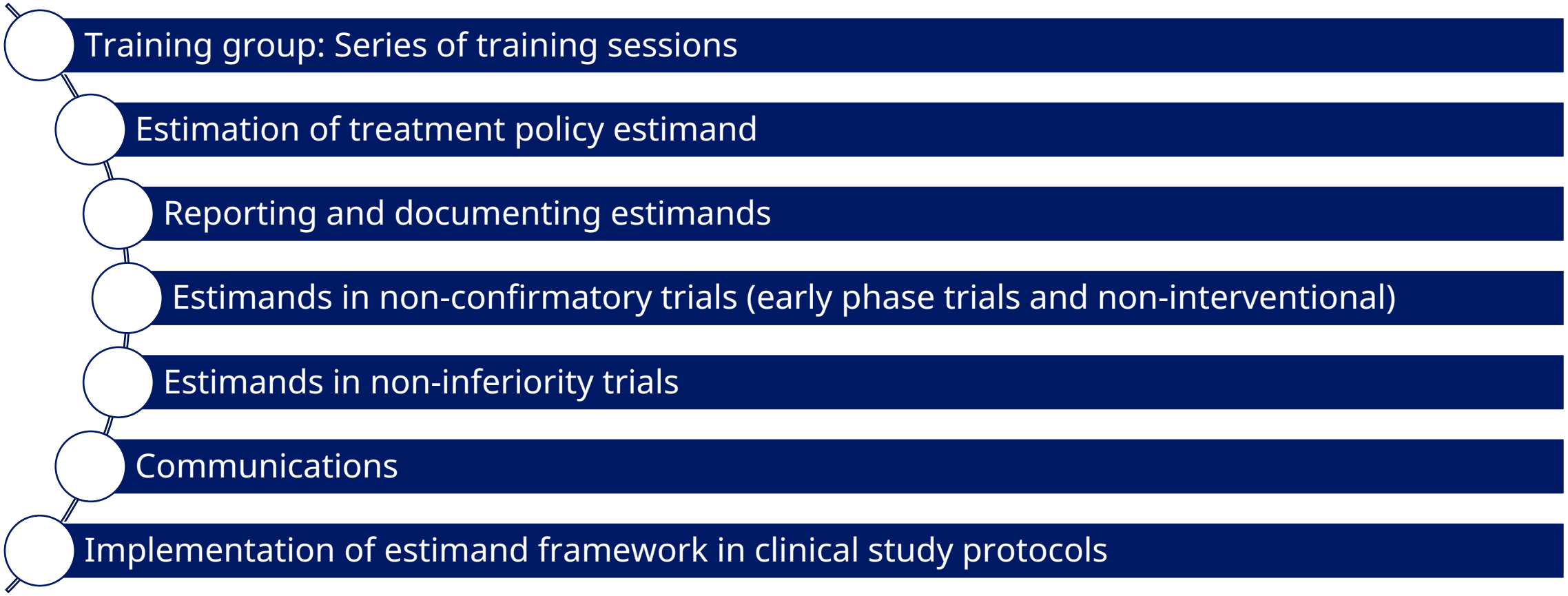
Institution	Member
AMGEN	Mary Elliott-Davey
astellas	Antonia Morga
AstraZeneca	David Wright
BAYER	Vivian Lanius
Boehringer Ingelheim	James Bell
Chiesi	Stefano Vezzoli
CONSILIUM Salmonson & Hemmings	Rob Hemmings*
EUROPEAN MEDICINES AGENCY	Lorenzo Guizzaro
GILEAD	Susanne Crowe
gsk	**Chrissie Fletcher+**
	Tricia Byers
	Millie Wang (C)
idorsia	Carrie Lie
Independent consultant	Oliver Keene
IQVIA	Maria Efstathiou

Institution	Member
janssen	Stefan Englert
LEO	Christian Pipper
	Kyle Raymond
Lilly	Pepa Polavieja
Lundbeck	**Nanco Hefting+** (C)
	Mette Josiassen
medac	Michael Tribanek
Medicines & Healthcare products Regulatory Agency	Khadija Rantell
MERCK	Armin Schueler
METRONOMIA	Volker Schoder
mundipharma	Nick Manamley
NOVARTIS	Melanie Wright
novo nordisk®	Helle Lynggaard
	Rikke Mette Agesen (C)

Institution	Member
Pfizer	Maria Dilleen
	Rod Junor (C)
PPD Part of Thermo Fisher Scientific	Sue McKendrick
	Nikolay Stoyanov (C)
PT Stat Consulting	Paul Terrill
Roche	Judith Anzures-Cabrera
SERVIER	Estelle Lambert
ucb	Christian Loesch
	Katsumi Yoshida
	Amel Besseghir+
UCL	Brenan Kahan
	Ian White

+Co-Lead *Adhoc member C = Clinician

EIWG sub-teams



Training webinars based on case studies

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

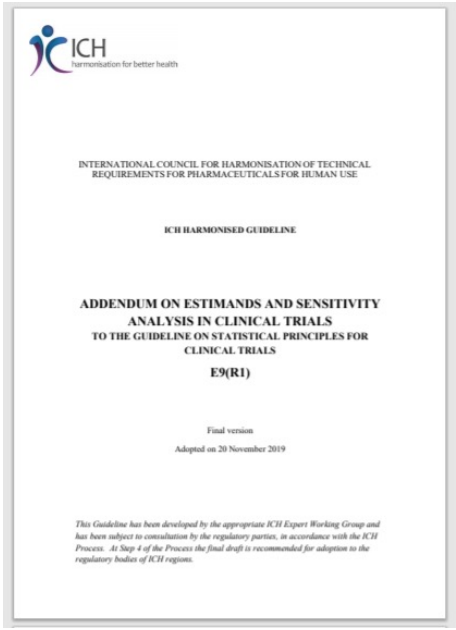
- First January 2021: *PIONEERing Estimands in Clinical Development webinar* **(HERE)**
- Second June 2021: *Estimands in Oncology – How and Why* **(HERE)**
- Third November 2021: *Estimands from trial planning to publication in medical journals: The ETHOS trial* **(HERE)**

- Video-on-Demand (psiweb.org) in the "Collection" filter choose "The Estimands Academy for Trial Teams"

- More webinars to come!

Why a sub-team on implementation in protocol templates?

- ICH E9(R1) does not give any guidance to how to implement and document estimands
- Perceived as a statistical topic – need to emphasise implications for other parts of protocol


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

Adopted on 20 November 2019

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

- Only one template available with estimands addressed
  - TransCelerate common protocol template

TransCelerate BIOPHARMA INC.

- ICH M11, expected to be released for public consultation in June 2022 and finalised in 2023
  - EIWG commented on early versions regarding the estimand framework

ICH
harmonisation for better health

Final Concept Paper

ICH M11: Clinical electronic Structured Harmonised Protocol (CeSHarP) dated 14 November 2018

Endorsed by the Management Committee on 15 November 2018

Initial considerations

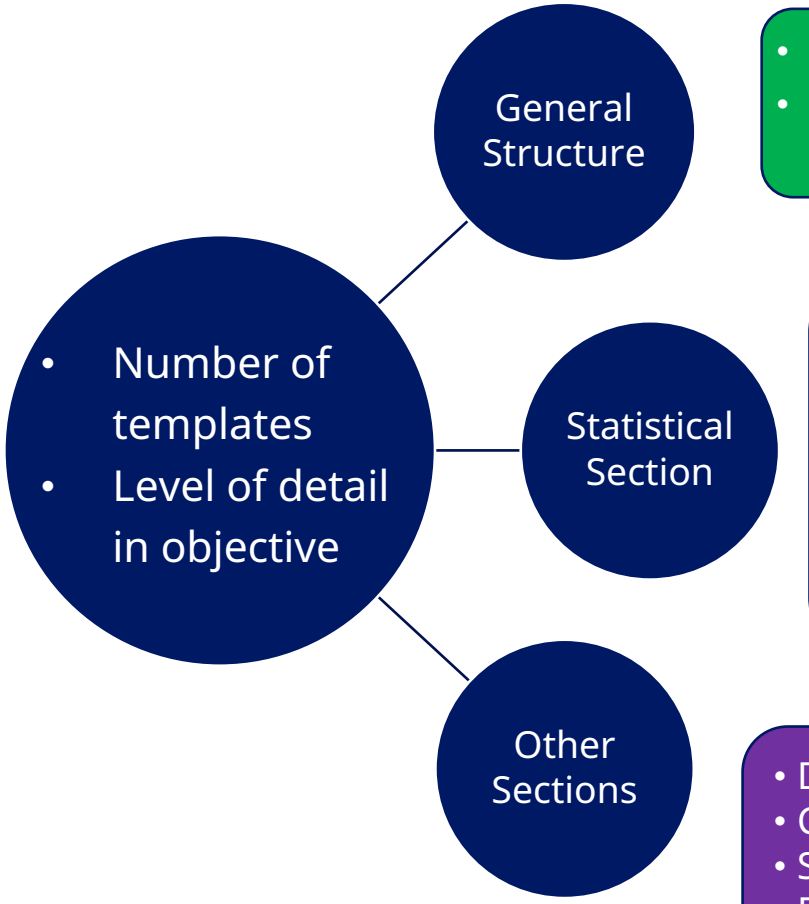
Number of templates

- Estimands not mandatory for all types of trials
  - One template fits all versus separate templates for trials with or without estimands

Level of detail in objectives

- Detailed Clinical Objective, Bell et al 2021
  - Estimand attributes addressed in objective
- Less detailed (“ICH E8(R1)”)
  - Clinical question of interest/estimand attributes need to be specified

Initial considerations, downstream challenges



- Where to describe estimands and their rationale?
- Structure around objectives or estimands versus structure around endpoints

- Align main analysis with estimand or objective
- Distinguish between intercurrent events & missing data
- Data points selection & implementation of intercurrent events strategies
- Distinction between sensitivity & supplementary analyses
- Sample Size estimation

- Design
- Conduct including Schedule of Activities and collection of data
- Study intervention
- Discontinuation of intervention
- Withdrawal from study

General Structure

Pre-ICH E9(R1):

- Structure endpoint-centred
- Estimands attributes scattered across different sections and intercurrent events not explicitly mentioned

IMPACT

Change of mindset:
Focus on all estimand attributes

RECOMMENDATIONS

- Estimands described early on with all attributes
- Analysis sections structured around objectives or estimands

How to write and document Estimands?

Pre-ICH E9(R1):

- Objectives most often unspecific in alignment with ICH E8(R1)
- Focus on linking objectives and endpoints

IMPACT

Change of mindset:
Need for clarity
Estimands vs. endpoints

RECOMMENDATIONS

- Detailed clinical objective – direct linking
- Less detailed objective
  - Layman
  - Bullet list of attributes
  - Clear link between objectives and estimands (table **or** textual)
- Rationale
- Naming

Statistical Section

Pre-ICH E9(R1):

- Unclear which question the main analysis addressed
- Sensitivity analyses a mixture of unrelated competing analyses
- Intercurrent events not separated from missing data

IMPACT

Change of mindset:
Transparency

RECOMMENDATIONS

- Main analysis with (sub)sections for sensitivity and supplementary analyses
- Distinction between intercurrent events and missing data
  - Separate intercurrent events section

Statistical Section: Supplementary Analysis

Pre-ICH E9(R1):

- No distinction between sensitivity and supplementary analyses

IMPACT

Change of mindset:

Transparency

RECOMMENDATIONS

Different understanding of what a supplementary analysis is:

- Compared to main, a supplementary analysis targets:
  - The same estimand?
  - A different estimand?
  - Either same or different (reflected in draft ICH E9(R1))

Statistical Section: Participants and Data Points

Pre-ICH E9(R1):

- Data points selection usually not described
- In ICH E9, “Analysis Set” refers to the set of participants whose data are to be included in an analysis

IMPACT

Change of mindset:
Participant level
versus
data level

RECOMMENDATIONS

- Specification of both data points and participants per estimand
- No consensus on best implementation approach:
  - Analysis Sets section
  - Separate section on statistical implications of intercurrent events and their strategies
  - In relevant analysis section

Statistical Section: Sample Size Calculation

Pre-ICH E9(R1):

- Number of completers needed calculated and sample size adjusted according to expected extent of missing data

IMPACT

Change of mindset:
Intercurrent events to be considered

RECOMMENDATIONS

- Specification of
  - Expected frequency of each of them by intervention
  - Impact on effect size and precision
- Estimands in reference studies to be mentioned

Other Sections

Pre-ICH E9(R1):

- Risk of misalignment between underlying clinical question of interest and design & conduct
- Discontinuation of intervention implied study withdrawal

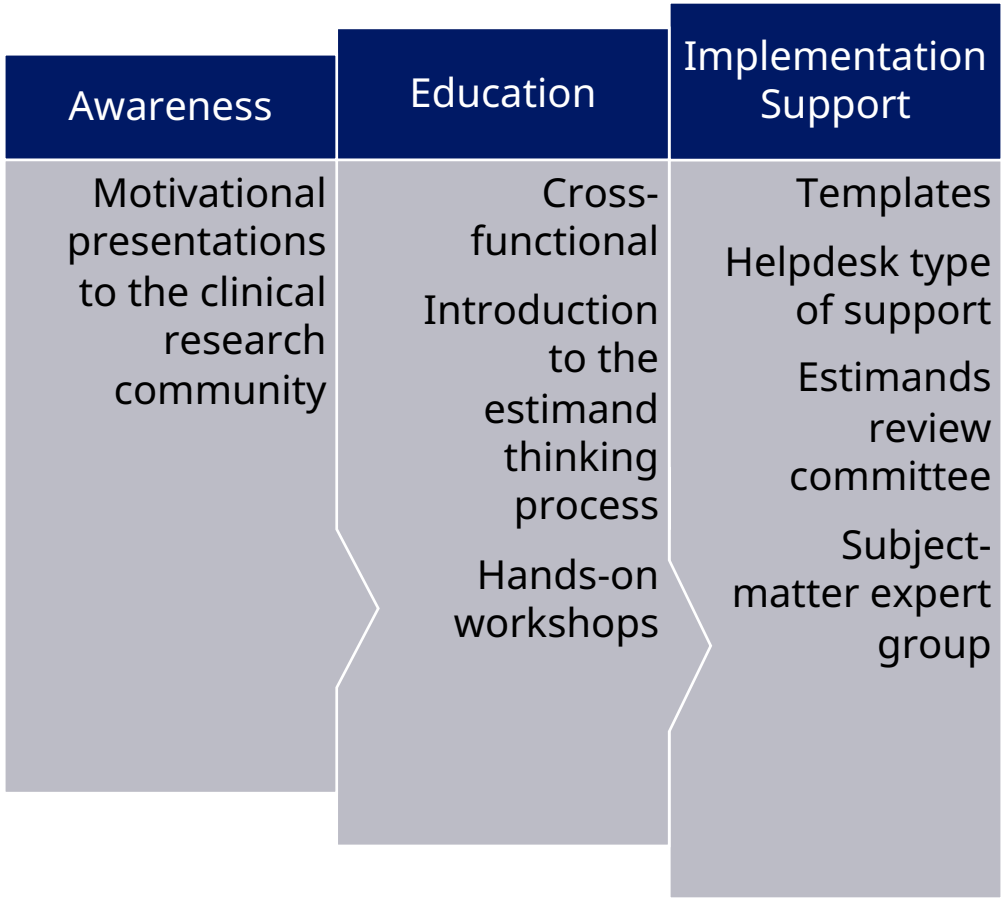
IMPACT

Change of mindset:
Transparency needed
to ensure consistency

RECOMMENDATIONS

- Instructional text to remind design and conduct sections to align with DCOs/estimand(s)
- Distinction between intervention discontinuation and study withdrawal

Training and Support within Companies



Key recommendations

- Implement estimand framework in all studies
- Define estimands in objectives section in high-level terms and add details in a separate section
- Name your estimands for ease of referencing
- Describe the clinical question of interest to engage non-statisticians, if less detailed objective is used
- Describe rationale for the choice of key estimands
- Align study design and conduct with defined estimands, including e.g., collection of details on intercurrent events and study interventions
- Differentiate between
  - discontinuation of intervention and study withdrawal
  - intercurrent events and missing data

Summary

- TransCelerate Common Protocol Template is the only publicly available template today including estimand framework
- ICH M11 Clinical electronic Structured Harmonised Protocol (CeSHarP) is expected to be released in 2023

- Estimands and objectives are the backbone of the study

- Estimands implementation is challenging

- Clarifications on analysis set and supplementary analysis needed

- Strategy for implementation within companies is key

References

- ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials (2019). E9-R1_Step4_Guideline_2019_1203.pdf (ich.org)
- ICH E9(R1) training slides: E9(R1) Training Material - PDF_0.pdf (ich.org)
- ICH E9 Statistical Principles for Clinical Trials (1998). GUIDELINE FOR GOOD CLINICAL PRACTICE (ich.org)
- ICH E8(R1) General Considerations for Clinical Studies (2021). Microsoft Word - E8-R1_Guideline_Step4_2022_0204 (ich.org)
- ICH M11 Clinical electronic Structured Harmonised Protocol (CeSHarP). ICH Official web site : ICH
- TransCelerate BioPharma INC. Clinical Content & Reuse Solutions; 2021. Common Protocol Template (CPT). Available from https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/.
- Bell J, Hamilton A, Sailer MO and Voss F. *The detailed clinical objectives approach to designing clinical trials and choosing estimands.* Pharmaceutical Statistics. 2021;1-13.
- Helle Lynggaard, James Bell, Christian Lösch, Amel Besseghir, Khadija Rantell, Volker Schoder, Vivian Lanius. *Principles and Recommendations for Incorporating Estimands into Clinical Study Protocol Templates,* 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.* Therapeutic Innovation & Regulatory Science 2022. https://doi.org/10.1007/s43441-022-00402-3