EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Estimand framework (regulatory perspective)

Session 2: Innovative trial designs and estimands

CDDF Multi-Stakeholder Workshop

Presented by Theodor Framke on 18 September 2023
Data Analytics and Methods Task Force

Disclaimer

The views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

The presenter does not have any conflict of interests.

Outline

1. Introduction to Estimands
2. Estimands (in Oncology)
3. Implementation

Acknowledgements

Juanjo Abellan, Lorenzo Guizarro, Florian Lasch, Frank Pétavy

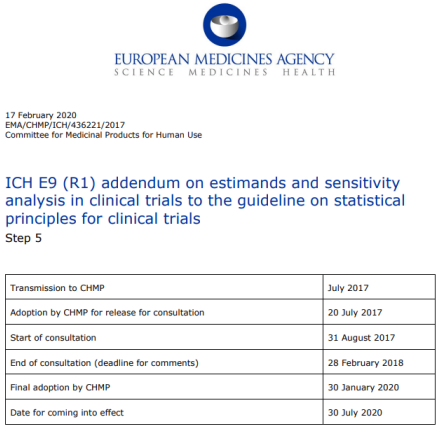
Introduction to Estimands

https://pixabay.com/photos/boy-book-reading-literature-read-5731001/

Background and History

What is ICH E9(R1) about?

- Addendum to ICH E9 (statistical principles)
- It outlines the **estimand** concept: Structured framework for the formulation of clinical trial objectives, design, conduct, analysis and interpretation
- Common terminology for treatment effect needed: *intercurrent events*, *strategies*, *attributes*
- Consequences if not taken into account: e.g. wrong interpretation of results
- ICH E9(R1) not yet implemented in daily practice
- ICH Training material available



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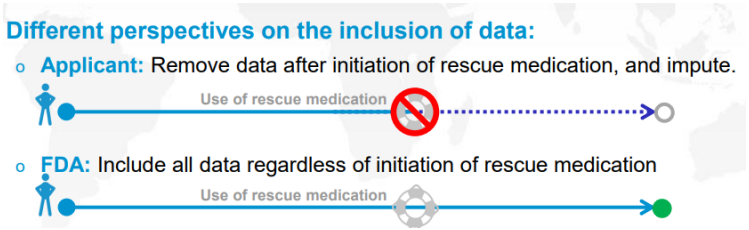
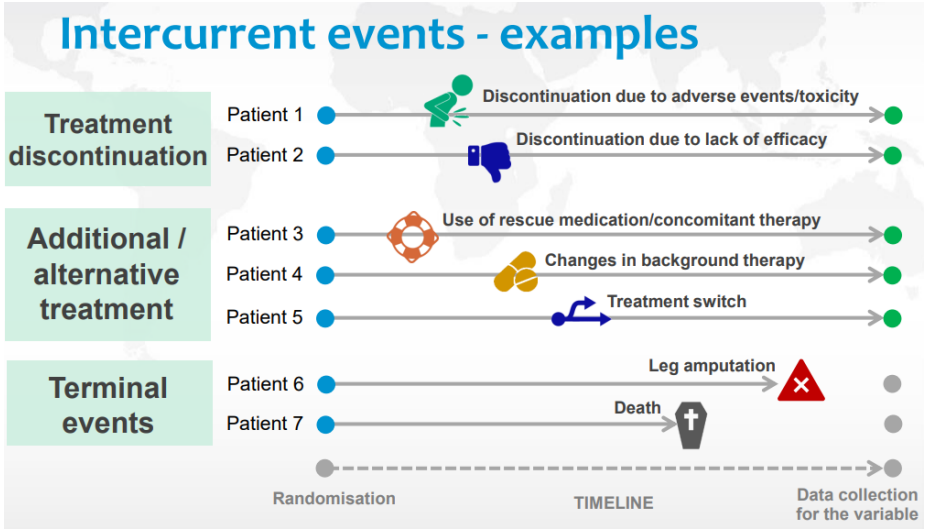
17 February 2020
EMA/CHMP/ICH/436221/2017
Committee for Medicinal Products for Human Use

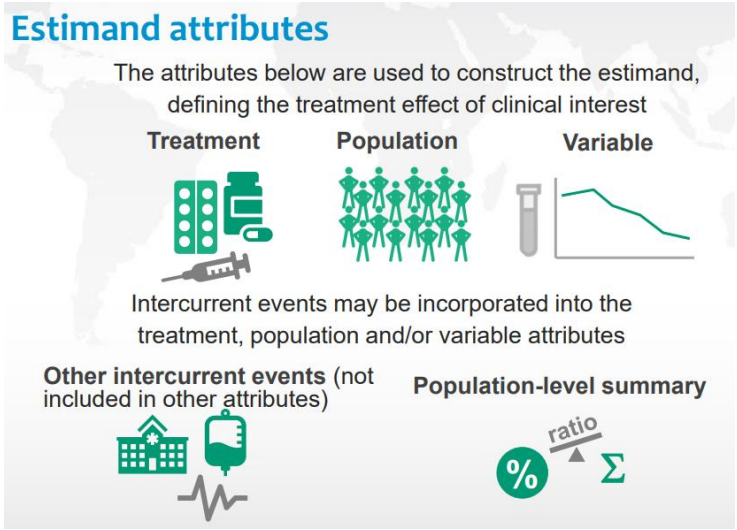
ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
Step 5

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017
End of consultation (deadline for comments)	28 February 2018
Final adoption by CHMP	30 January 2020
Date for coming into effect	30 July 2020



Estimands – What do you need to consider?





Strategies

Treatment Policy | Composite | Hypothetical | While-on-treatment | Principal strata

https://database.ich.org/sites/default/files/E9%28R1%29%20Training%20Material%20-%20PDF_0.pdf

Estimands (in Oncology)

https://pixabay.com/photos/thermometer-medications-tablets-1539191/

ICH E9(R1) addressed gaps and lack of clarity in clinical trials

- Lack of logical connectivity between trial objectives, design, conduct, analysis and interpretation
- Insufficient clarity in how objectives of clinical trials linked to estimation of treatment effect parameters of interest (i.e., estimands)
- Misalignment between “missing data” analysis methods and treatment effects of interest
- Misunderstanding of the term “sensitivity analysis”

Estimands in Oncology

- Traditional way of analysing data: intention-to-treat (ITT) principle
- Trials may not be free from post-randomisation confounding
- Usually *time-to-event* outcomes (i.e. PFS, OS,…), Hazard Ratio
- It is not just censoring – need to consider *Intercurrent Events*
- Treatment switching?, Toxicities?, Background therapy?, Progression?, Subsequent therapies?,…

Ongoing discussion

Ann Intern Med. 2013 Oct 15;159(8):560-2. doi: 10.7326/0003-4819-159-8-201310150-00709.

Randomized trials analyzed as observational studies

Miguel A Hernán, Sonia Hernández-Díaz, James M Robins

PMID: 24018844 PMCID: PMC3860874 DOI: 10.7326/0003-4819-159-8-201310150-00709

Free PMC article

Pharm Stat. 2021 Jul;20(4):793-805. doi: 10.1002/pst.2108. Epub 2021 Mar 8.

Estimands in hematologic oncology trials

Steven Sun [1], Hans-Jochen Weber [2], Emily Butler [3], Kaspar Rufibach [4], Satrajit Roychoudhury [5]

Affiliations + expand

PMID: 33686762 DOI: 10.1002/pst.2108

Pharm Stat. 2022 Jan;21(1):150-162. doi: 10.1002/pst.2158. Epub 2021 Oct 3.

Estimands for overall survival in clinical trials with treatment switching in oncology

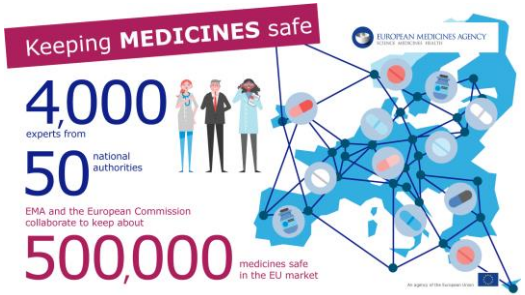
Juliane Manitz [1], Natalia Kan-Dobrosky [2], Hannes Buchner [3], Marie-Laure Casadebaig [4], Evgeny Degtyarev [5], Jyotirmoy Dey [6], Vincent Haddad [7], Fei Jie [8], Emily Martin [1], Mindy Mo [9], Kaspar Rufibach [10], Yue Shentu [11], Viktoriya Stalbovskaya [12], Rui Sammi Tang [13], Godwin Yung [14], Jiangxiu Zhou [15]

Affiliations + expand

PMID: 34605168 DOI: 10.1002/pst.2158

Implementation of Estimands

Overview of activities in the Regulatory Network



ACT EU and **Methodology Working Party**

ACT EU is an initiative to **transform the EU clinical research environment** in support of medical innovation and better patient

Methodology Working Party

- Established in 2022, includes biostatistics, modelling and simulation, pharmacokinetics, pharmacogenomics, and real-world evidence
- 3-year Work Plan foresees work on estimands
- Implementation group expanded from EMA to Regulatory Network

Marketing Authorisation and Scientific Advice

- Assessment templates updated to use estimand language
- Input to discussion on Recurrent Events
- Uptake of estimands in European Public Assessment Reports (EPAR) (example)

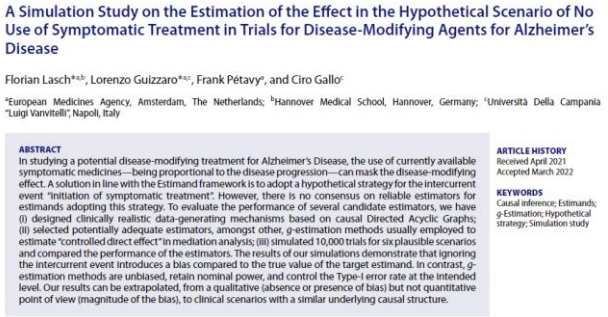
Why is this important for you?

- Instead of asking „*Is Endpoint XYZ acceptable?*", you could broaden this question to estimands
- Will lead to additional clarity, better basis for discussion
- Early adoption of the concept at the planning stage will pay off later

Research

- Regulators are actively contributing to the ongoing discussion
- Assessment of strategies and estimators, e.g. in CNS and COVID-19
- Ongoing work on non-inferiority and equivalence trials, to be published soon

Examples



A Simulation Study on the Estimation of the Effect in the Hypothetical Scenario of No Use of Symptomatic Treatment in Trials for Disease-Modifying Agents for Alzheimer's Disease

Florian Lasch[a,b], Lorenzo Guizzaro[a,c], Frank Pétavy[a], and Ciro Gallo[c]

[a]European Medicines Agency, Amsterdam, The Netherlands; [b]Hannover Medical School, Hannover, Germany; [c]Università Della Campania "Luigi Vanvitelli", Napoli, Italy

ABSTRACT

In studying a potential disease-modifying treatment for Alzheimer's Disease, the use of currently available symptomatic medicines—being proportional to the disease progression—can mask the disease-modifying effect. A solution in line with the Estimand framework is to adopt a hypothetical strategy for the intercurrent event "initiation of symptomatic treatment". However, there is no consensus on reliable estimators for estimands adopting this strategy. To evaluate the performance of several candidate estimators, we have (i) designed clinically realistic data-generating mechanisms based on causal Directed Acyclic Graphs; (ii) selected potentially adequate estimators, amongst other, g-estimation methods usually employed to estimate "controlled direct effect" in mediation analysis; (iii) simulated 10,000 trials for six plausible scenarios and compared the performance of the estimators. The results of our simulations demonstrate that ignoring the intercurrent event introduces a bias compared to the true value of the target estimand. In contrast, g-estimation methods are unbiased, retain nominal power, and control the Type-I error rate at the intended level. Our results can be extrapolated, from a qualitative (absence or presence of bias) but not quantitative point of view (magnitude of the bias), to clinical scenarios with a similar underlying causal structure.

ARTICLE HISTORY
Received April 2021
Accepted March 2022

KEYWORDS
Causal inference; Estimands; g-Estimation; Hypothetical strategy; Simulation study

https://www.tandfonline.com/doi/full/10.1080/19466315.2022.2055633

MAIN PAPER

WILEY

Estimators for handling COVID-19-related intercurrent events with a hypothetical strategy

Florian Lasch[1,2] | Lorenzo Guizzaro[1,3]

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[2]Hannover Medical School, Hannover, Germany
[3]Medical Statistics Unit, Università della Campania "Luigi Vanvitelli", Napoli, Italy

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Abstract

The COVID-19 pandemic has affected clinical trials across disease areas, raising the questions how interpretable results can be obtained from impacted studies. Applying the estimands framework, analyses may seek to estimate the treatment effect in the hypothetical absence of such impact. However, no established estimators exist. This simulation study, based on an ongoing clinical trial in patients with Tourette syndrome, compares the performance of candidate estimators for estimands including either a continuous or binary variable and applying a hypothetical strategy for COVID-19-related intercur-

https://onlinelibrary.wiley.com/doi/epdf/10.1002/pst.2244

Implementation in Guidlines

- ICH E9(R1) has a knock-on effect
  - … ICH guidelines such as M11, E20
  - … EMA publishes Guidelines for Therapeutic Areas (TA)
- All Therapeutic Areas may have a different background, traditions developed over time, etc.
- But still… a discussion on estimands is needed

Example

ICH Member

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26 October 2022
EMA/CHMP/ICH/778801/2022
Committee for Human Medicinal Products

ICH M11 template
Step 2b

Transmission to CHMP	3 October 2002
Adoption by CHMP	13 October 2022
Release for public consultation	26 October 2022
Deadline for comments	26 February 2023

Comments should be provided using this template. The completed comments form should be sent to ich@ema.europa.eu

Implementation in therapeutic Guidelines

Implementation status

- Large number of Therapeutic Guidelines from EMA
- Different stages
  - No estimand concept yet
  - Partially implemented
  - Fully implemented
- Revisions are ongoing

Recent examples from 2023

286 **4.2.1. Target of estimation in depression**

287 The scientific question(s) of interest, i.e. what the trial seeks to address, and consequently the
288 target(s) of estimation (estimand) should be clearly specified. Trial planning, design, conduct, analysis,
289 and interpretation must be aligned with the estimand. Reference is made to ICH E9 (R1) addendum on
290 estimands and sensitivity analysis in clinical trials (EMA/CHMP/ICH/436221/2017).

291 Relevance and (expected) frequency of intercurrent events may differ between different therapeutic
292 settings and consequently influence the definition of a relevant (primary) estimand. Different

Guideline on clinical investigation of medicinal products in the treatment of depression

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Link to document

Estimation of the treatment effect (estimands)

The primary target should be the estimation of a treatment effect based on the difference in HbA1c from baseline to the end-of-trial (or another predefined timepoint) between the test compound and a control treatment. The actual adherence to treatment as well as intercurrent events should be reflected in the estimation of the effect. The main expected intercurrent events to be considered include treatment discontinuation, additional medications and rescue medication.

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus
CPMP/EWP/1080/00 Rev.2

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Link to document

Summary

Trying to precisely define the objective

- Estimands have come and will stay
- This is not just *from statisticians for statisticians*
- The concept is rolled out to further guidance documents. Become acquainted with the concept – it will be needed

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Any questions?

Further information

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