The interdisciplinary process for implementing the estimand framework, with examples from Major Depressive Disorder

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Disclaimers

- Nanco Hefting, MSc, Pharm is an employee of H. Lundbeck A/S

- Elena Polverejan, PhD is an employee of Johnson & Johnson Innovative Medicine

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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

Implementation status:

ANVISA, Brazil - In the process of implementation; Date: 1 December 2023;

COFEPRIS, Mexico - Not yet implemented;

EC, Europe - Implemented; Date: 30 July 2020; Reference: EMA/CHMP/ICH/436221/2017

EDA, Egypt - Implemented; Date: 1 January 2019;

FDA, United States - Implemented; Date: 11 May 2021; Reference: Posted on FDA, US website

HSA, Singapore - Implemented; Date: 1 November 2019; Reference: HSA, Singapore webpage: Guidance documents for clinical trials

Health Canada, Canada - Implemented; Date: 21 July 2020; Reference: File #: 20-109237-45

MFDS, Republic of Korea - In the process of implementation; Date: 22 December 2023;

MHLW/PMDA, Japan - In the process of implementation;

MHRA, UK - Implemented; Date: 1 July 2020;

NMPA, China - Implemented; Date: 25 January 2022; Reference: NMPA, China Announcement No. 16 (2021)

SFDA, Saudi Arabia - Implemented; Date: 10 August 2023;

Swissmedic, Switzerland - Implemented; Date: 30 November 2019;

TFDA, Chinese Taipei - Implemented; Date: 9 February 2021; Reference: Updated-Announcement for ICH Guidelines Recognition List

TITCK, Türkiye - Not yet implemented;

https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

Estimands in Regulatory Guidelines and Templates

- FDA:
  - Chronic Rhinosinusitis with Nasal Polyps
  - Acute Myeloid Leukemia
  - Eosinophilic Esophagitis
- EMA:
  - Depression
  - Alzheimer’s disease
  - Diabetes mellitus
  - Ulcerative Colitis
- EMA: Day 80 assessment report - Clinical template with guidance
- EMA: Assessment of SmPC section 5.1 4 - A Guide for Assessors of Centralised Applications

Goal of this Presentation

- Why is the estimand framework useful?
- What do I need to know to implement it in a trial?

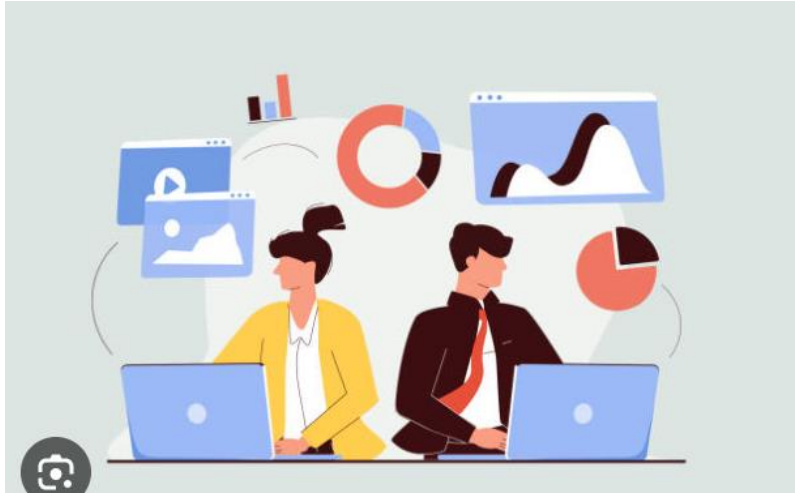
WHAT type of treatment effect is of interest in a trial,

to **WHOM**,

and **WHY**

HOW to estimate that effect
through trial design and analysis

Questions



Can we read in protocols and published papers:

- Easy to understand clinical questions of interest connected to trial objectives?
- What is the treatment effect of interest? - Which treatments are compared, in whom, using what outcome and summary, and accounting for what happens during patient journeys?
- Why are the selected questions relevant to the trial stakeholders?

Clinicians and Statisticians:

- Do we know how to interact with other functions on setting trial objectives and formulating clinical questions of interest?
- Do we speak the same language?

ISCTM Estimands and Missing Data WG

Main Objective: Develop an approach to the process of applying the estimand framework that is relevant to many types of studies across clinical areas and illustrate the approach with examples of specific Central Nervous System (CNS) studies.

Members:

Clinical, Statistical, FDA/EMA Regulatory

First Output

Published paper: https://link.springer.com/article/10.1007/s43441-023-00524-2

Published Paper

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Paper available open access due to ISCTM sponsorship

In Memoriam - Pilar Lim

- Co-chair of the ISCTM Estimands and Missing Data WG (2016-2023)
- Approx. 30-year career at Johnson & Johnson, leading the statistical work on numerous compounds in Neuroscience
- Active in external statistical and psychiatric communities, often organizing and leading sessions on statistical methodology in Neuroscience area
  - 2022 Chair of the Mental Health Statistics Section of the American Statistical Association
- Great statistician, teacher, mentor, leader, and colleague

Outline

- Practical guide for implementation of the estimand framework
  - Process step by step
- Two examples based on Major Depressive Disorder (MDD):
  - Short-term monotherapy treatment
  - Maintenance monotherapy treatment
- Summary and conclusions

Recommended Steps in Applying the Estimand Framework
ISCTM Estimand WG

Identify the trial stakeholder(s)

State decision(s) to be made by each stakeholder

Define trial objective(s)

Under each trial objective supporting main decision making:

Formulate the clinical question of interest

Define the corresponding estimand

Justify the utility of the selected question and corresponding estimand to the specific stakeholder(s).

Clinical Trial – Stakeholder(s) and Examples of Decisions to be Made

Health authority agencies	• trial contributes substantial evidence of short-term efficacy for a new treatment • new treatment is effective as maintenance treatment after an initial short-term response
Company developing a new treatment	• trial provides enough evidence of efficacy for a treatment to justify continuing its development
Payers	• prescribing a new drug is more clinically effective over a long-term period than prescribing another well-established drug • trial contributes substantial evidence of clinically meaningful patient-level benefit
Physicians and patients	• prescribe or take a treatment

Trial Objective

- A trial objective is a general statement of what supports a stakeholder's decision.
- It should mention:
  - type of assessment (e.g., of superiority, non-inferiority, Go/No Go etc.) supporting the stakeholder decision making
  - treatment condition(s) that are being compared or investigated
  - target population for treatment
  - outcome of interest (endpoint)
- Example:

  To assess the superiority of experimental treatment versus alternative treatment on endpoint for target population

Clinical Question of Interest

Introduces **in a concise way** what is the treatment effect of interest to the corresponding trial stakeholder(s).

It is best formulated using **natural, non-technical language**.

It is linked to a trial objective

It is paired with a formal, detailed definition of the corresponding estimand.

Needs justification:

How answering this question would support stakeholder decision making?

Formulating a Clinical Question of Interest

- Must consider the clinical context of use:
  - treatment condition(s) that are being compared or investigated
  - target population for treatment
  - outcome of interest (endpoint)
  - intercurrent events (ICEs) pertinent to the clinical context

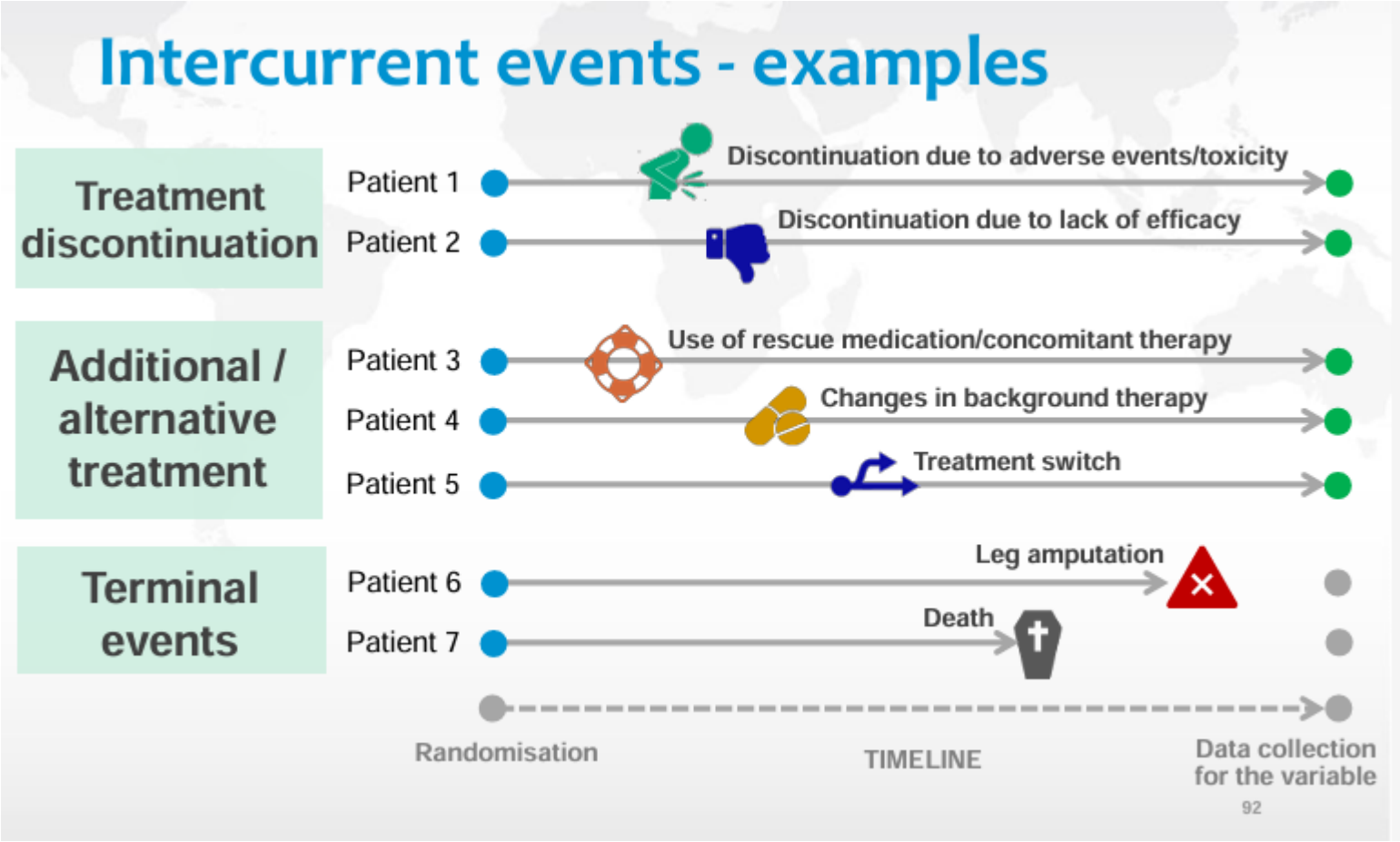
- Example:

  For a patient with MDD for whom acute drug monotherapy would be indicated, what would be the expected effect of being assigned drug X on depression severity at Week 8, were no other antidepressant medications available?

Intercurrent Events (ICEs)

ICH E9(R1) Addendum Definition: Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

Each identified ICE needs to be addressed by a strategy.



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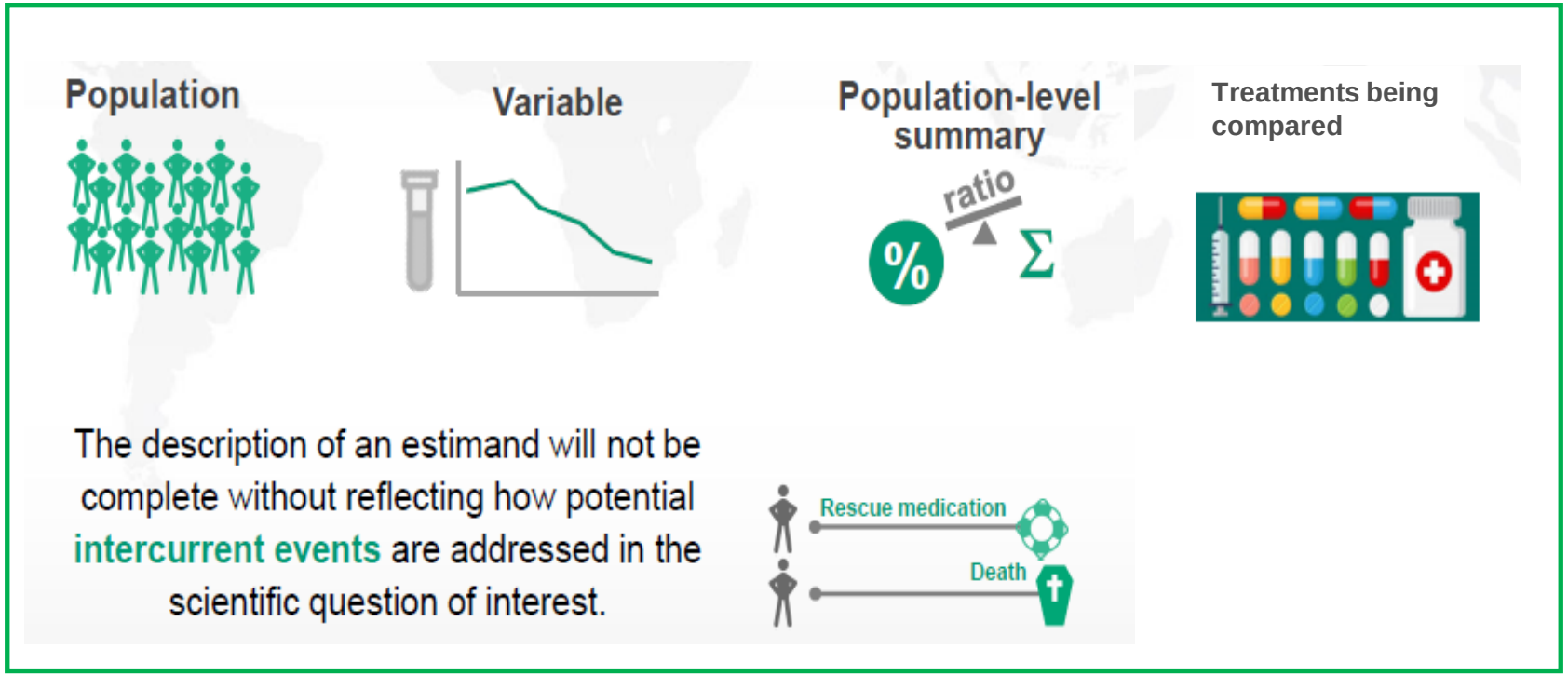
Defining An Estimand

- An estimand defines in detail what needs to be estimated to address a specific scientific question of interest.
  - –A description of the estimand includes **5 attributes**



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Strategies for Handling Intercurrent Events

- The strategies are chosen to **reflect the clinical question of interest** for **each intercurrent event**.
  - Different strategies will often be used for different intercurrent events within the same estimand.
  - The names of the strategies are just for ease of reference. What is essential is to make clear what the strategy for each intercurrent event is, once the estimand is constructed.
  - The relevance of each strategy will depend on the **therapeutic and experimental context**.
  - Not all strategies will be equally acceptable for regulatory decision making!

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Question of Interest vs Intercurrent Event (ICE) Strategies

EXAMPLE: Consider the ICE of initiation of rescue medication in a placebo-controlled trial

	ICE Strategy
Effect of assigning Drug X vs. Placebo, **regardless of initiation of rescue medication** (i.e., effect of assigning **Drug X+rescue vs. Placebo+rescue**)	**Treatment Policy**
Effect of assigning Drug X vs. Placebo, **as if rescue medication is not available**	**Hypothetical**
Effect of assigning Drug X vs. Placebo **in patients who would not initiate rescue if prescribed Drug X**	**Principal Stratum**
Effect of assigning Drug X vs. Placebo, **where patients who initiate rescue are considered treatment failures**	**Composite Variable**
Effect assigning Drug X vs. Placebo, **while patients remain on treatment and don't initiate rescue**	**While on Treatment**

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Example 1 - Short-term monotherapy treatment in MDD

(Estimand 1 in Polverejan et al, 2023)

Stakeholder	
Decision to be made	
Objective	
Intercurrent Events	
Question of interest	

Example 1 - Short-term monotherapy treatment in MDD

Stakeholder	Health Authority Agency
Decision to be made	Determine if the study contributes substantial evidence of short-term efficacy for drug X
Objective	To assess the superiority of drug X versus placebo on short-term symptom reduction when given as monotherapy treatment in MDD patients
Intercurrent Events	
Question of interest	

Example 1 - Short-term monotherapy treatment in MDD

Stakeholder	Health Authority Agency
Decision to be made	Determine if the study contributes substantial evidence of short-term efficacy for drug X
Objective	To assess the superiority of drug X versus placebo on short-term symptom reduction when given as monotherapy treatment in MDD patients
Intercurrent Events	Treatment Discontinuation (Tx DC), Starting other pharmacological treatments for MDD
Question of interest	For a patient with MDD for whom acute drug monotherapy would be indicated, what would be the expected effect of **being assigned** drug X on depression severity at Week 8, were no other antidepressant medications available?

Example 1 – Estimand Definition

Estimand Definition

(The names of attributes in bold are per ICH E9(R1) document and should not be changed.)

Treatment condition of interest vs Alternative treatment condition: Assignment to drug X vs placebo, at the selected dose and frequency of administration

Population: Patients with a diagnosis of MDD in a current major depressive episode with at least moderate symptom severity

Variable: Change from baseline to Week 8 in the total score of the 17-item version of Hamilton Depression Rating Scale (HDRS)

Population-level summary: Difference in treatment means

Intercurrent events and Corresponding Strategies:

Intercurrent Event	Strategy	Description
Tx DC	Treatment-policy	Strategy targeting the effect of treatment assignment, regardless of the occurrence of this ICE
Starting other pharmacological treatments for MDD	Hypothetical	A scenario is envisaged in which the event would not have occurred because other pharmacological treatments for MDD are not available

Example 1 – Utility to Stakeholder

Utility of this question of interest and corresponding estimand to Stakeholder	Answering this question requires an estimate of the expected effect of treatment under trial conditions as close as possible to real-world use. The evaluation of the assignment to either drug X vs placebo (so of being assigned or not monotherapy drug X) is of practical importance as treatment discontinuation occurs not only in trials but also in clinical practice and a treatment effect in an ideal condition, where there is perfect compliance, would be unrealistic. On the other hand, in the monotherapy context, the effect of other antidepressants that might be used following assignment to either drug X or placebo is not of interest.

Example 1 – Trial Design and Key Implementation Elements

Trial design	Parallel, double-blind, placebo controlled, randomized trial design
Key implementation elements needed to address this estimand	Efficacy data after Tx DC are directly relevant to this estimand and efforts should be made to collect them. Efficacy data after starting other pharmacological treatments for MDD are not relevant to this estimand, but trial protocols should plan to collect the information because the data may be relevant to a different estimand. The date of occurrence of each ICE should be clearly documented in eCRF.

Example 2 - Maintenance monotherapy treatment in MDD

(Estimand 5 in Polverejan et al, 2023)

Stakeholder	
Decision to be made	
Objective	
Intercurrent Events	
Question of interest	

Example 2 - Maintenance monotherapy treatment in MDD

Stakeholder	Health Authority Agency
Decision to be made	Determine if the study provides substantial evidence that drug X is effective as a maintenance treatment for MDD after an initial short-term response
Objective	To assess the superiority of monotherapy drug X versus placebo in preventing relapse in patients with MDD who have shown a stable response to initial treatment with drug X and for whom continuing monotherapy would be clinically acceptable
Intercurrent Events	
Question of interest	

Example 2 - Maintenance monotherapy treatment in MDD

Stakeholder	Health Authority Agency
Decision to be made	Determine if the study provides substantial evidence that drug X is effective as a maintenance treatment for MDD after an initial short-term response
Objective	To assess the superiority of monotherapy drug X versus placebo in preventing relapse in patients with MDD who have shown a stable response to initial treatment with drug X and for whom continuing monotherapy would be clinically acceptable
Intercurrent Events	Tx DC due to reasons other than those included in the definition of relapse
Question of interest	For a patient with MDD who experienced a stable response to initial treatment with drug X and for whom continuing monotherapy would be clinically acceptable, what is the effect of the **assignment to** continuing versus discontinuing drug X on the occurrence of relapse up to 1 year?

Example 2 – Estimand Definition

Estimand Definition	
(The names of attributes in bold are per ICH E9(R1) document and should not be changed.)	**Treatment condition of interest vs Alternative treatment condition:** Assignment to continuation of drug X vs switching to placebo, at the selected dose and frequency of administration **Population:** Patients with a diagnosis of MDD, who have shown a stable response to initial treatment with drug X and for whom continuing monotherapy would be clinically acceptable **Variable:** Time to relapse up to Year 1, where relapse is defined as the first occurrence of 1) a total score >X on the 17-item version of the HDRS, 2) hospitalization due to depressive or MDD-associated symptoms (including suicidal ideation or behavior), 3) treatment discontinuation due to lack of efficacy and/or suicidal ideation or behavior, 4) switching to or adding other pharmacological treatment for MDD **Population-level summary:** Hazard ratio of drug X versus placebo **Intercurrent events and Corresponding Strategies:**

Intercurrent Event	Strategy	Description
Tx DC due to reasons other than those included in the definition of relapse	Treatment-policy	Strategy targeting the effect of treatment assignment, regardless of the occurrence of this ICE

Example 2 – Continued

Utility of this question of interest and corresponding estimand to Stakeholder	The evaluation of the assignment to continuation of drug X versus switching to placebo is of practical importance as decisions on treatment continuation in remitted patients need to be informed.
Trial design	
Key implementation elements needed to address this estimand	

Example 2 – Continued

Utility of this question of interest and corresponding estimand to Stakeholder	The evaluation of the assignment to continuation of drug X versus switching to placebo is of practical importance as decisions on treatment continuation in remitted patients need to be informed.
Trial design	Randomized withdrawal trial design, where patients who can be stabilized on drug X in a run-in open-label phase are then randomized into a parallel, DB, placebo-controlled phase, comparing stabilized dose of drug X to placebo
Key implementation elements needed to address this estimand	Efficacy and hospitalization data after Tx DC due to other reasons than included in the definition of relapse are directly relevant to this estimand as occurrence of relapse can still be assessed, and efforts should be made to collect them. The date of occurrence of each ICE should be clearly documented in eCRF.

Estimand Examples – ISCTM paper

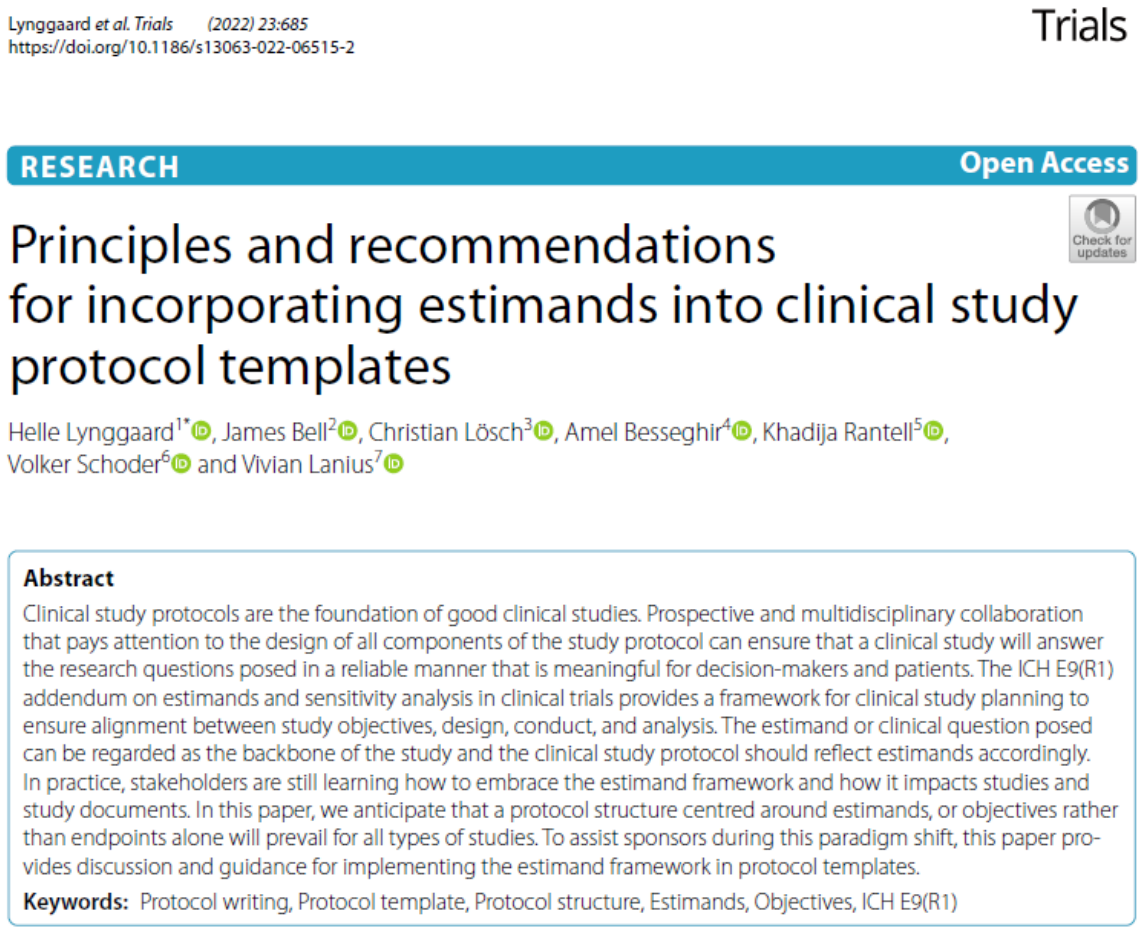
Estimand	Context	Main Stakeholder	Strategies for Intercurrent Events
1	Short-term monotherapy treatment in MDD	Health Authority Agency	Treatment Policy, Hypothetical
2		Pharmaceutical company for internal decision-making	Hypothetical
3		Payers	Composite Variable, Hypothetical
4		Prescribers or patients	Principal Stratum
5 (5-alt)	Maintenance monotherapy treatment for MDD	Health Authority Agency	Treatment Policy
6	Short-term add-on/adjunctive treatment in MDD	Health Authority Agency	Treatment Policy, Hypothetical
7a and 7b	Maintenance add-on/adjunctive treatment in patients with treatment resistant depression	Payers	While on treatment, Treatment Policy

Template – **Estimator/Statistical Analysis** Specifications

Estimand and Estimator aligned analysis set	Participant Analysis Set: Data Included: Data handling
Data not used (or not existing)	
Missing data	
Assumptions for data not used and missing and for model of main estimator	Guided by the defined estimand, including strategies used for intercurrent events
Main Estimator/Statistical Analysis	
Sensitivity Estimator(s), including what assumptions change from the Main Estimator	• Stress-test main estimator assumptions, targeting same estimand • Describe what assumptions of the main estimator changed • Ideally, stress-test one assumption at a time
Analysis used for decision making	

Documentation of Estimands

- The ICH E9(R1) Addendum recommends at a minimum that estimands for all trial objectives that are likely to support regulatory decisions (such as those related to primary and key secondary endpoints) be defined and specified explicitly in the trial protocol.
  - ICH M11 protocol template
  - TransCelerate Common Protocol Template v9.0
- Phase 2 and 3 trials should document the estimands in the protocol.
- Estimand framework could be useful and applicable to other types of trials, such as Phase 1 and 4 trials, observational studies, validation studies etc.



Lynggaard *et al. Trials* (2022) 23:685
https://doi.org/10.1186/s13063-022-06515-2

Trials

RESEARCH Open Access

Principles and recommendations for incorporating estimands into clinical study protocol templates

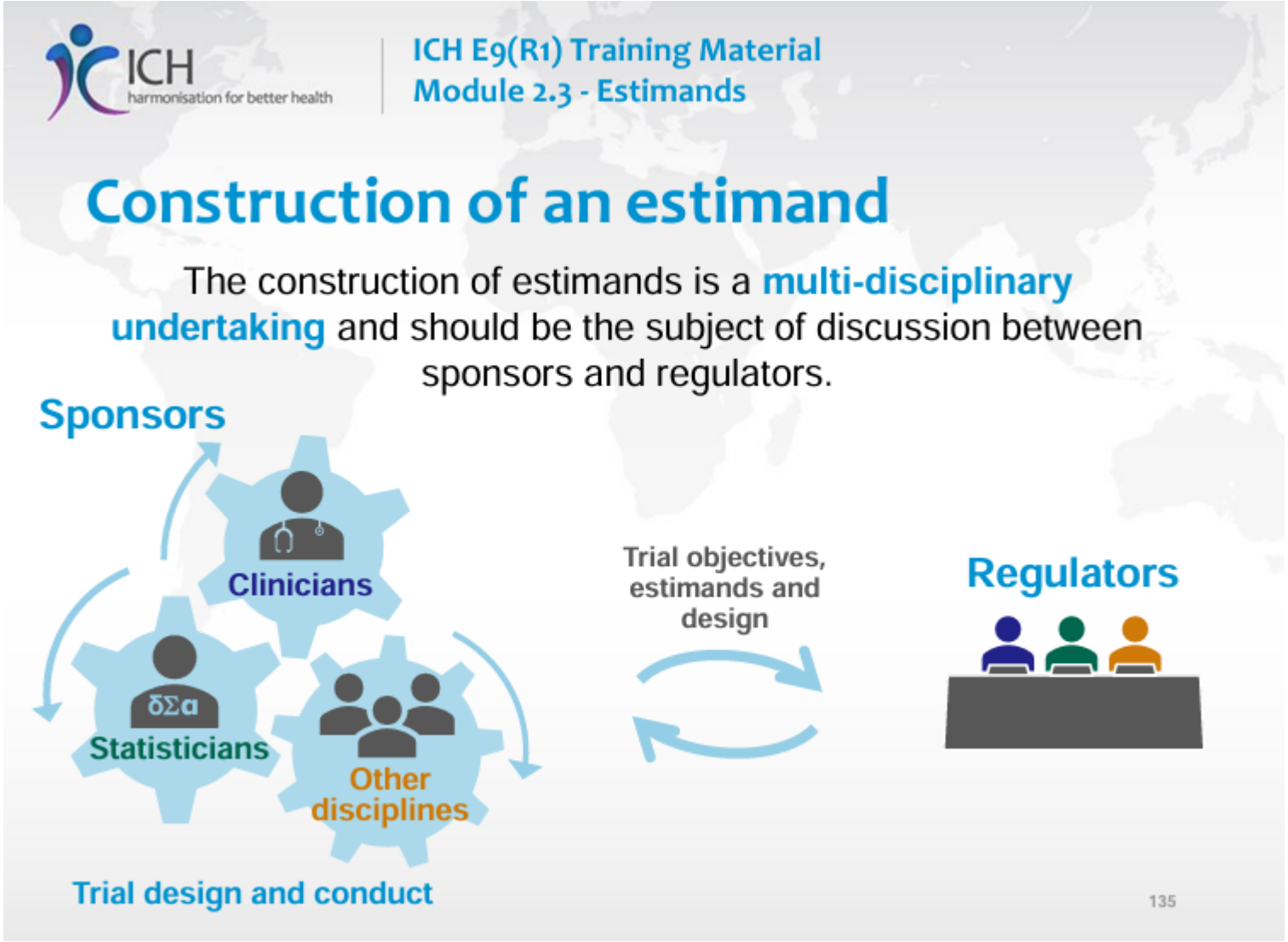
Helle Lynggaard[1*], James Bell[2], Christian Lösch[3], Amel Besseghir[4], Khadija Rantell[5], Volker Schoder[6] and Vivian Lanius[7]

Abstract

Clinical study protocols are the foundation of good clinical studies. Prospective and multidisciplinary collaboration that pays attention to the design of all components of the study protocol can ensure that a clinical study will answer the research questions posed in a reliable manner that is meaningful for decision-makers and patients. The ICH E9(R1) addendum on estimands and sensitivity analysis in clinical trials provides a framework for clinical study planning to ensure alignment between study objectives, design, conduct, and analysis. The estimand or clinical question posed can be regarded as the backbone of the study and the clinical study protocol should reflect estimands accordingly. In practice, stakeholders are still learning how to embrace the estimand framework and how it impacts studies and study documents. In this paper, we anticipate that a protocol structure centred around estimands, or objectives rather than endpoints alone will prevail for all types of studies. To assist sponsors during this paradigm shift, this paper provides discussion and guidance for implementing the estimand framework in protocol templates.

Keywords: Protocol writing, Protocol template, Protocol structure, Estimands, Objectives, ICH E9(R1)

Interdisciplinary Process to Implement the Estimand Framework



Collaboration across disciplines needed:

- Defining estimands requires close **cooperation** between clinician and statistician
- Other disciplines should be consulted as well, as needed (regulatory, clinical operations, health economics, market access, medical affairs, safety)

Summary and Conclusions

- Implementation of the estimand framework can be facilitated through:
  - Implementation process with clear steps
  - Examples
  - Disease specific regulatory guidelines
  - Templates for protocols and other trial and regulatory documents
- Important:
  - Interdisciplinary collaboration essential
  - Early engagement with Health Authority Agencies
- It’s a journey:
  - Let’s continue learning and promoting the estimand framework!