ISCTM
International Society for CNS Clinical Trials and Methodology

22nd Annual Scientific Meeting

Estimands and Missing Data Working Group

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Meeting Moderators: Elena Polverejan, PhD, Nanco Hefting, MSc, Pharm

- 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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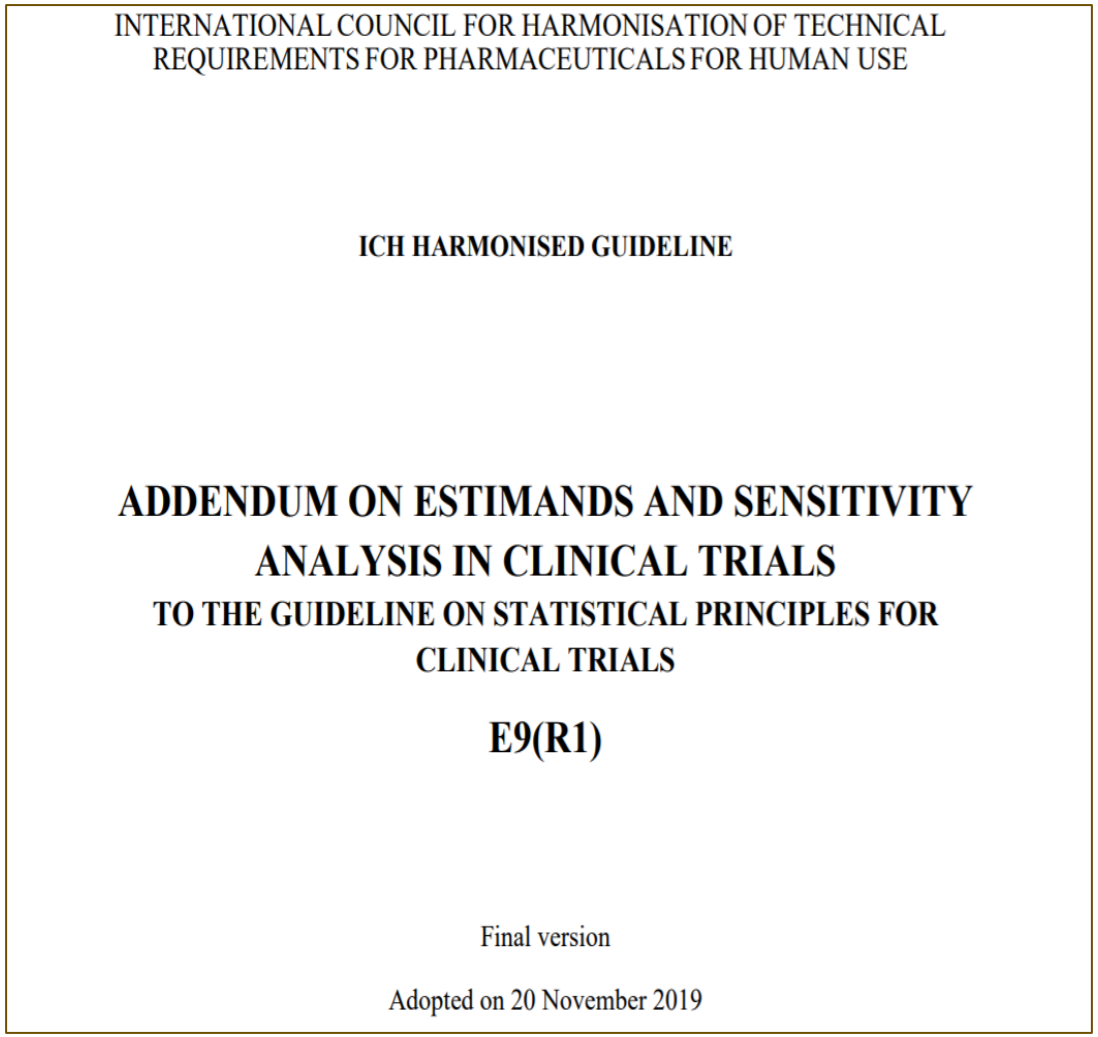
Views expressed by authors in this discussion do not represent the views of their employer companies

Outline

- Background: ICH E9(R1) and ICH M11 protocol template
- ISCTM Estimands and Missing Data WG:
  - Previous work
  - Current collaboration with the Psychedelics WG
- Discussion: How to improve multi-disciplinary collaborations when applying the estimand framework
  - Examples from psychedelics trials


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

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

ICH M11 Protocol Template

Table of Contents

Aligned with ICH E9 and E9(R1)

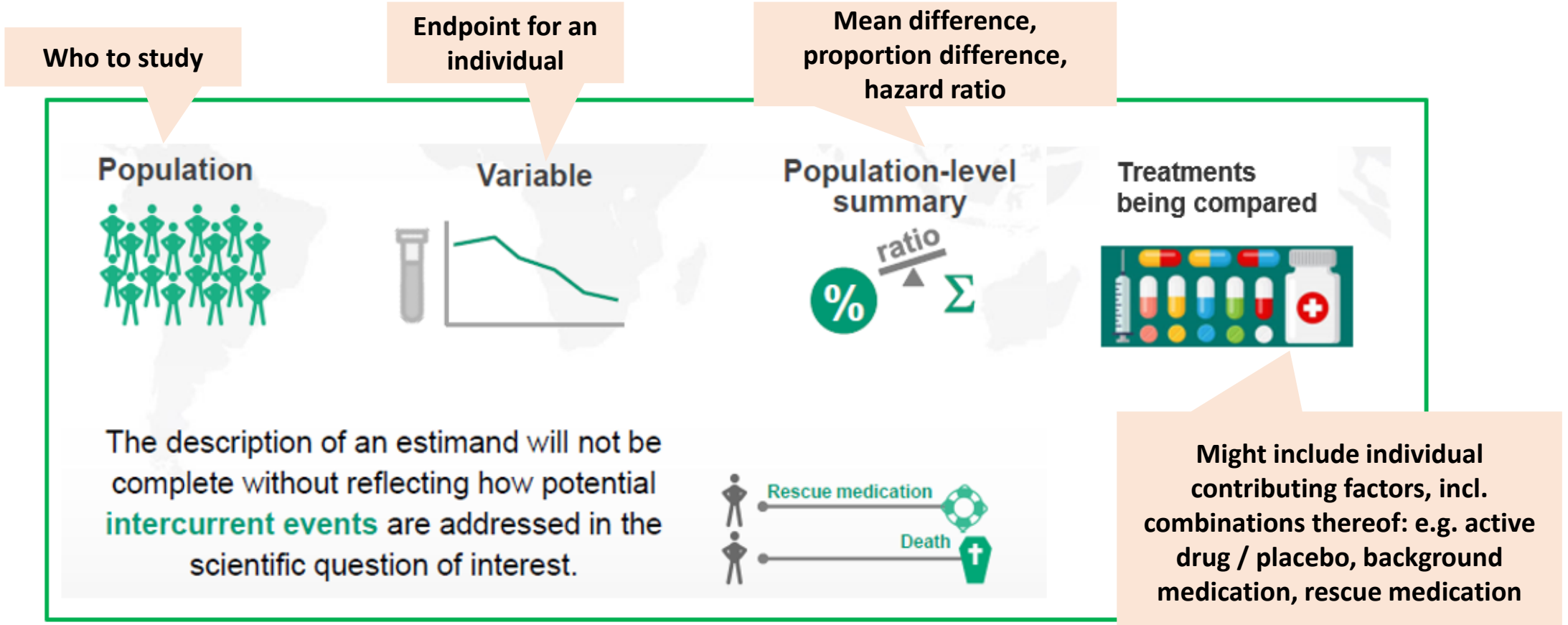
'Estimands' instead of 'endpoints'

Estimand aligned rationale, design, and analysis

https://ich.org/page/multidisciplinary-guidelines#11

Estimand - Five Attributes

An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective.



ISCTM Estimands and Missing Data WG

Initial 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:

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

ISCTM WG
Recommended Steps in Applying the Estimand Framework

- Identify the stakeholder(s) for whom the estimand is being defined
- State decision(s) to be made by each stakeholder
- Define objective(s)
- Under each objective supporting main decision making:
  - Formulate the clinical question of interest:
    - Consider the clinical context
    - Consider potential intercurrent events (ICEs) and how they relate to the question
  - Define the corresponding estimand
  - Justify the utility of the selected question and corresponding estimand to the specific stakeholder(s).

Collaboration with the ISCTM Psychedelics WG

Untangling the specific methodological issues of psychedelics' trials using the estimand framework:

- Potential for functional unblinding
- High expectancy bias
- Lack of appropriate comparator
- Use of psychological support/ psychotherapy along with study drug
- Intermittent (few) treatment vs daily dosing, including implications for demonstrating durability of effect and long-term study designs

Discussion:

How to improve multi-disciplinary collaborations when applying the estimand framework?

Trial Objective

- It should at least 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 new treatment versus placebo on endpoint for target population

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 and how they are addressed
- Example:

  For patients with MDD for whom acute drug monotherapy would be indicated, what is the expected effect of initiating monotherapy drug X on depression severity at Week 8, that is not attributable to other antidepressant medications?

Treatment Condition(s) – Compared or Investigated

- Include treatment condition (regimen) of interest vs control (i.e. alternative treatment condition)
- Need precise definition of treatment: dosage, frequency, route, duration, if applicable: sequence, background/subsequent/rescue therapy
- Any major deviation should be reflected in an intercurrent event
- Clinical input vital – e.g. on precise definition of treatment, interpretation of allowed/prohibited medications or therapies

Example Psychedelics:

- Psychedelic medicine + psychotherapy

vs

- Psychotherapy

Question for discussion:

What if the patient starts using antidepressants after the psychedelic treatment session?

Target Population for Treatment

- Patients targeted by the clinical question
- Is the target population reflected by the trial participants?

Example Psychedelics:

To assess re-treatment, the population could include patients who had some level of response to the first treatment and who might benefit from re-treatment

Question for discussion:

Any differences versus standard relapse prevention trials?

Endpoint

Outcome of interest

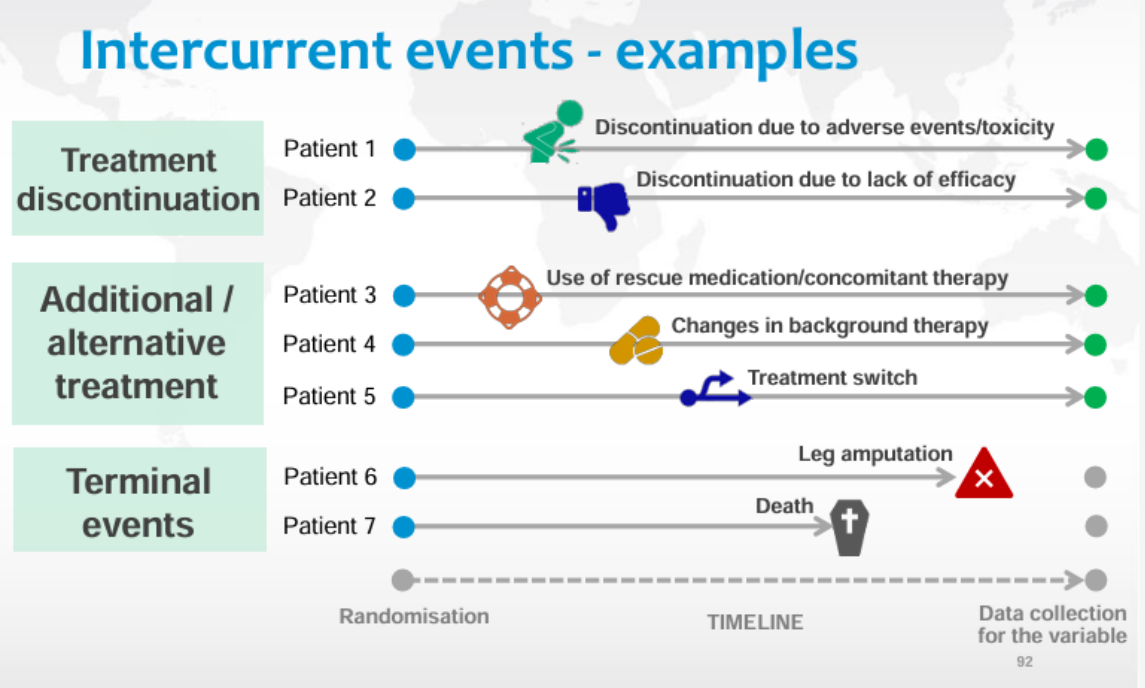
- A value that can be measured in individual patients (defined at patient level) that is required to address the clinical question of interest.
  - Do not use proportions or other group summaries in the endpoint definition.
- Examples
  - Continuous: Change from baseline to Week [X] in [an outcome]
  - Binary: [Response] at Week [XX] (yes/no), where a patient is considered to achieve response if …
  - Time to event: Time from [treatment assignment/initiation] to first occurrence of an [event]
- Should include all ICEs described by the composite strategy.

Example Psychedelics in MDD/TRD:

Clinical remission at Week 12 (yes/no), where a patient is considered to have achieved clinical remission if the following conditions are met: MADRS score ≤10 (or HAM-D ≤7) and no intercurrent events are experienced prior to Week 12.

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.



Example Psychedelics:

Any major changes to the pre-specified psychotherapy regimen, such as a change in therapist, needing additional or missing psychotherapy sessions

From ICH E9(R1) training

17

From Clinical Question of Interest to ICE Strategies

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

ICE Strategy

Effect of assigning/initiating **Drug X+rescue vs. Placebo+rescue** → **Treatment Policy**

Effect of assigning Drug X vs. Placebo, **that is not attributable to rescue medication** → **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 of assigning Drug X vs. Placebo, **while patients remain on treatment and don't initiate rescue** → **While on Treatment**

Question for discussion:

How can potential questions be formulated for the ICE of treatment discontinuation?

18