



ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials

Training Module 3 – Generic example

Addendum to ICH E9 – Statistical Principles for Clinical Trials

ICH E9(R1) Expert Working Group
December 2021

Disclaimer

This presentation includes the authors' views on theory and practice regarding estimands and sensitivity analysis in clinical trials.

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Introduction note

These slides were produced as training material to accompany the ICH E9(R1) addendum.

The intention is to support the scientific community in the comprehension of a new framework to define estimands based on the trial objective and considering intercurrent events. For this purpose, most of the content of this addendum is presented in a practical fashion, accompanied by examples dealing with estimands and sensitivity analysis in clinical trials, based on the experience of Expert Working Group members.

The training material is divided in three main modules: module 1 (summary), module 2 (comprehensive slide deck) and module 3 (generic example). Module 2 is composed by 6 submodules that correspond to sections A.1 to A.6 of the addendum.

Training modules

- Module 1: Summary
- Module 2: Comprehensive slide deck
 - Module 2.1: Introduction
 - Module 2.2: Framework
 - Module 2.3: Estimands
 - Module 2.4: Impact on trial design and conduct
 - Module 2.5: Impact on trial analysis
 - Module 2.6: Documenting estimands and sensitivity analysis
- **Module 3: Generic example**

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Estimands and Sensitivity Analysis

A thinking process

A thinking process...

- ① Therapeutic setting and intent of treatment determining a trial objective
- ② Identify intercurrent events
- ③ Discuss strategies to address intercurrent events
- ④ Construct the estimand(s)
- ⑤ Align choices on trial design, data collection and method of estimation
- ⑥ Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions
- ⑦ Document the chosen estimands

A thinking process...

- ① **Therapeutic setting and intent of treatment determining a trial objective**
- ② Identify intercurrent events
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① Therapeutic setting and intent of treatment determining a trial objective

- The **therapeutic setting** and the **intent of treatment** will determine the trial objective.
- An understanding of the clinical relevance of the treatment in a therapeutic setting includes the **disease or condition under study and the clinical context**.
- **Diagnosis, treatment and prevention** are different intents of treatment and will determine different trial objectives.
- Together these will start to shape the **estimand attributes (Module 2.3)**.

① Therapeutic setting and intent of treatment determining a trial objective

Example – Drug X

- **For example, a treatment might be intended for a chronic non-life-threatening condition.**
 - The development programme might aim to investigate the effect of treatment to control a sign or symptom of the disease.
 - This will give rise to initial thoughts for the target population and the variable. For example, consider a variable measured monthly on a continuous scale (e.g., systolic blood pressure, SBP, after 6 months in hypertension).
 - A clear description of the treatment and other concomitant medications, background and rescue treatments helps identifying intercurrent events.

A thinking process...

- ① Therapeutic setting and intent of treatment determining a trial objective
- ② **Identify intercurrent events**
- ③ Discuss strategies to address intercurrent events
- ④ Construct the estimand(s)
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② Identify **intercurrent events**

Intercurrent events 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.

Intercurrent events definition, ICH E9(R1)



Events that preclude the observation of the variable (e.g. death) should not be confused with missing data resulting from loss to follow-up that can occur in a clinical trial.

② Identify intercurrent events

- **Common intercurrent events**

- Events that can affect the interpretation of measurements:
 - Treatment discontinuation, possibly but not necessarily identified as multiple separate intercurrent events distinguished by reason (e.g., treatment discontinuation due to lack of efficacy, due to toxicity,...);
 - Use of additional or alternative medication, perhaps distinguished by type and / or reason, e.g.: change in background or concomitant therapy, switching between treatments of interest; in the context of a trial these can also be labelled as rescue or prohibited treatments;
- Death and other terminal events.

- **Other clinical events** (e.g. stroke in a trial measuring motor function) can also be intercurrent events if they affect the existence or the interpretation of the variable of interest.

② Identify intercurrent events



Address each intercurrent event that will affect the interpretation of the trial results, not only the most frequently occurring

Example – Drug X

- Examples of intercurrent events that might be foreseen
 1. Treatment discontinuation.
 2. Use of additional or alternative medication (that will impact measurements of SBP).

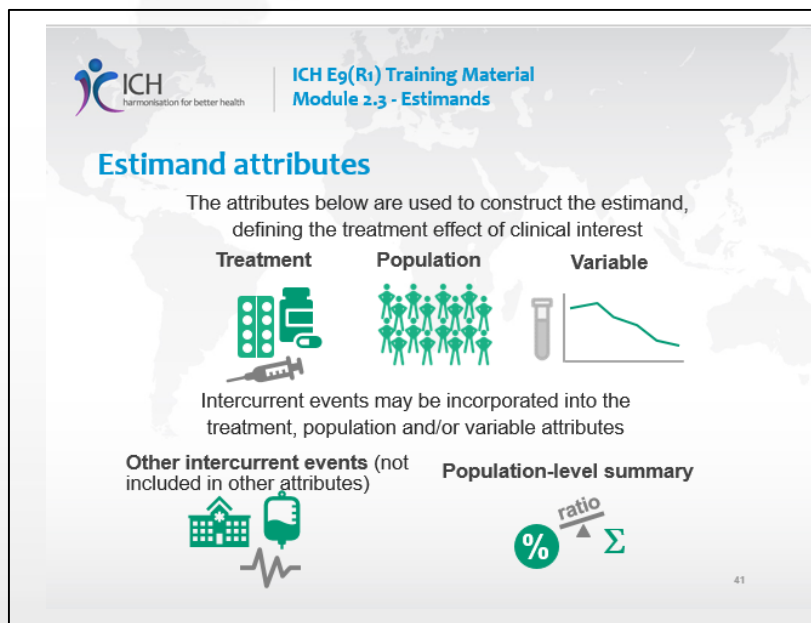
A thinking process...

- 1 Therapeutic setting and intent of treatment determining a trial objective
- 2 Identify intercurrent events
- 3 Discuss strategies to address intercurrent events**
- 4 Construct the estimand(s)
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③ Discuss strategies to address intercurrent events

• Discuss...

- Consider different strategies to address these two intercurrent events (Module 2.3 slides 21-39).
- Reflect how to account for intercurrent events through the estimand attributes (see Module 2.3, illustrated on the following slides).



ICH E9(R1) Training Material
Module 2.3 - Estimands

Estimand attributes

The attributes below are used to construct the estimand, defining the treatment effect of clinical interest

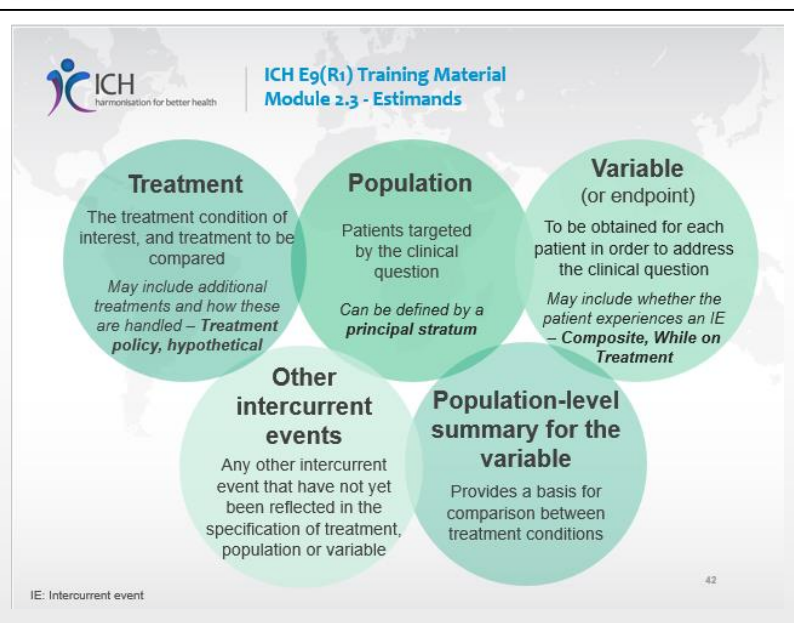
Treatment	Population	Variable
		
Intercurrent events may be incorporated into the treatment, population and/or variable attributes		

Other intercurrent events (not included in other attributes)

Population-level summary

ratio $\frac{\%}{\Sigma}$

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ICH E9(R1) Training Material
Module 2.3 - Estimands

IE: Intercurrent event

- Treatment**
The treatment condition of interest, and treatment to be compared
May include additional treatments and how these are handled – Treatment policy, hypothetical
- Population**
Patients targeted by the clinical question
Can be defined by a principal stratum
- Variable (or endpoint)**
To be obtained for each patient in order to address the clinical question
May include whether the patient experiences an IE – Composite, While on Treatment
- Other intercurrent events**
Any other intercurrent event that have not yet been reflected in the specification of treatment, population or variable
- Population-level summary for the variable**
Provides a basis for comparison between treatment conditions

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③ Discuss strategies to address intercurrent events

- Choose each strategy to reflect the **clinical question of interest**. Each choice of strategy should be **driven by the trial objective** and **not by the preferred choice of estimator**. Consider:
 - Is what is to be estimated **clinically relevant for decision making**?
 - Can an estimate that is **reliable for inference** be obtained?
- The choice of strategy for each intercurrent event should be the subject of **multi-disciplinary discussion** within the sponsor's team, within the regulator's team and between sponsor and regulator.

③ Discuss strategies to address intercurrent events

Example – Drug X

Consider the possible strategies to address each intercurrent event

- Objective = **quantifying the effects of chronic treatment on SBP.**
- Intercurrent event (1) = **treatment discontinuation.**

Consider different strategies:

1. **Treatment policy:** to investigate a treatment effect at Month 6 regardless of whether or not the patients continue with treatment (as described in the treatment attribute).

③ Discuss strategies to address intercurrent events

Example – Drug X

2. **Hypothetical:** to investigate a treatment effect at Month 6 if all patients continue with treatment (specified in the treatment attribute).
3. **Composite:** to investigate a treatment effect at Month 6 where patients who discontinue treatment before Month 6 will be considered having experienced no effect, for example the treatment effect is established based on a composite variable requiring both a clinically meaningful change in SBP and continuation of treatment to Month 6 (specified in this example in the variable (or endpoint) attribute).

③ Discuss strategies to address intercurrent events

Example – Drug X

4. **While on treatment:** to investigate the effect of treatment while the patient continues to take their treatment rather than at a fixed time (i.e. 6 months) after initiation of treatment (specified in the variable attribute).
5. **Principal stratum:** to investigate the effect of treatment at Month 6 in the stratum of the population who would be able to continue treatment with drug X (specified in the population attribute).

③ Discuss strategies to address intercurrent events

Example – Drug X

Consider the possible strategies to address each intercurrent event

- Objective = **quantifying the effects of the chronic treatment on SBP.**
- Intercurrent event (2) = **use of additional or alternative medication that affects SBP.**

Consider different strategies:

1. **Treatment policy:** investigate the treatment effect at Month 6 regardless of whether or not the patient uses additional or alternative medication. This strategy will capture the effect of assigning patients to Drug X including potentially its effect on starting additional or alternative medication. Both the description of the treatment with Drug X and what is considered as an additional or alternative medication that would affect SBP should be defined in the treatment attribute).

③ Discuss strategies to address intercurrent events

Example – Drug X

2. **Hypothetical:** investigate the treatment effect at Month 6 if additional or alternative medication would not be available to patients. This strategy aims to capture the effect of drug X in the absence of additional or alternative medication (specified in the treatment attribute).
3. **Composite:** for example, the treatment effect is established based on a composite variable requiring a clinically meaningful change obtained without the use of additional or alternative medication at Month 6.

③ Discuss strategies to address intercurrent events

Example – Drug X

4. **While on treatment:** to investigate the effect of treatment before the point at which the patient uses additional or alternative medication (specified in the variable attribute).
5. **Principal stratum:** to investigate the effect of treatment at Month 6 in the stratum of the population who would not use any medication in addition to drug X (specified in the population attribute).

A thinking process...

- 1 Therapeutic setting and intent of treatment determining a trial objective
- 2 Identify intercurrent events
- 3 Discuss strategies to address intercurrent events
- 4 Construct the estimand(s)**
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④ Construct the estimand(s)

Example – Drug X

Select a preferred strategy for each intercurrent event:

- For illustration* we choose:
 - Treatment discontinuation → **Treatment policy (specified in the treatment attribute).**
 - Use of additional or alternative medication that affects SBP → **Hypothetical (specified in the treatment attribute).**

④ Construct the estimand(s)

Example – Drug X

Definition of the estimand:

Treatment: treatment condition of interest is Drug X regardless of whether or not the patient continues with Drug X and where additional or alternative medication was not available until Month 6; alternative treatment condition is placebo regardless of whether or not the patient continues with placebo and where additional or alternative medication was not available until Month 6.

Population: patients with uncontrolled hypertension.

Variable: change from baseline to Month 6 in SBP.

How to account for intercurrent events: n/a (already covered in treatment attribute).

Population-level summary for the variable: difference in means between treatment conditions.

④ Construct the estimand(s)

Example – Drug X

A description of the estimand might be*:

The difference in means for the change from baseline to Month 6 in SBP between treatment conditions (Drug X regardless of discontinuation and placebo regardless of discontinuation, both in the absence of additional or alternative medication) in patients with uncontrolled hypertension.

④ Construct the estimand(s)

Example – Drug X

Select a preferred strategy for each intercurrent event:

- As a second illustration* we choose:
 - Treatment discontinuation → **Treatment policy (specified in the treatment attribute).**
 - Use of additional or alternative medication that affects SBP → **Composite (specified in the variable attribute).**

④ Construct the estimand(s)

Example – Drug X

Definition of the second estimand:

Treatment: treatment condition of interest is Drug X regardless of whether or not the patient continues with it; alternative treatment condition is placebo regardless of whether or not the patient continues with it.

Population: patients with uncontrolled hypertension.

Variable: binary variable indicating a successful response if a clinically meaningful change from baseline to Month 6 in SBP is obtained without the use of additional or alternative medication.

How to account for intercurrent events: n/a (already covered in the treatment and variable attributes).

Population-level summary for the variable: difference in proportions between treatment conditions.

④ Construct the estimand(s)

Example – Drug X

A description of the estimand might be*:

The difference in proportions of treatment successes between treatment conditions (Drug X and placebo, regardless of discontinuation) in patients with uncontrolled hypertension whereby treatment success is defined as response at Month 6 in SBP without use of additional or alternative medication.

A thinking process...

- 1 Therapeutic setting and intent of treatment determining a trial objective
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⑤ Align choices on trial design, data collection and method of estimation

- In addition to choosing strategies to reflect the scientific question of interest, it is necessary to determine that an appropriate trial design and statistical analysis can be performed. Specifically:

- **Consider the data that need to be collected.**



- Difficulties in data collection following the occurrence of an intercurrent event are not necessarily a strong rationale to change an estimand or strategy.

- **Consider whether an estimate of the treatment effect can be derived that is reliable for decision making.**

⑤ Align choices on trial design, data collection and method of estimation



A balance might need to be struck between an estimand of greater clinical relevance estimated with an analytical approach that requires assumptions that are difficult to justify, and an estimand of less clinical relevance that can be estimated with an analytical approach requiring more justifiable assumptions. This will also depend on the extent to which sensitivity analysis can provide confidence in the reliability of the results.

⑤ Align choices on trial design, data collection and method of estimation

Example – Drug X

- A **randomised controlled trial** comparing Drug X to placebo is considered the most appropriate design to investigate the research question for both previously mentioned examples.
- **Consider the data that would need to be collected**, e.g. for the use of additional or alternative medication:
 - for a treatment-policy strategy it should be planned that **all measurements of SBP regardless of use of additional or alternative medication are collected** throughout the trial;
 - for a hypothetical strategy **the need to collect measurements of SBP after the use of additional or alternative medication** would depend on the estimator chosen.

⑤ Align choices on trial design, data collection and method of estimation

Example – Drug X

- Consider whether an estimate of the treatment effect can be derived that is reliable for decision making, e.g., for the use of additional or alternative medication:
 - for a **treatment-policy strategy** if all data are collected then analysis might rely on few assumptions. Otherwise, estimation will rely on model assumptions that require extensive sensitivity analysis.
 - for a **hypothetical strategy** some of the measurements of SBP cannot be observed under the treatment conditions of interest and the estimation will rely on model assumptions that require more extensive sensitivity analysis.

⑤ Align choices on trial design, data collection and method of estimation

Example – Drug X

- Consider whether an estimate of the treatment effect can be derived that is reliable for decision making, e.g. for the use of additional or alternative medication (continued):
 - for a **principal stratum strategy** estimation of a treatment effect by comparing outcomes in subsets defined by the observed occurrence of the intercurrent event will likely be confounded due to differing characteristics of the subjects in the various subsets.
 - for a **while on treatment strategy** particular care is needed when the occurrence and timing of an intercurrent event is related to treatment.



The extent of the assumptions and sensitivity analysis required in estimation might preclude the choice of a particular estimand.

⑤ Align choices on trial design, data collection and method of estimation

Example – Drug X

- **Estimand* (slide 28):** The difference in means for the change from baseline to Month 6 in SBP between treatment conditions (Drug X regardless of discontinuation and placebo regardless of discontinuation, both in the absence of additional or alternative medication) in patients with uncontrolled hypertension.
- Discuss and select **a method for estimation*** that is **aligned** to the estimand:
 - e.g., assuming all post-treatment discontinuation data were collected, ANCOVA with an appropriate imputation of the measurements after the patient uses additional or alternative medication, based on an adequately justified model.

Treatment policy component

Hypothetical component

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- 7 Document the chosen estimands

⑥ Identify **assumptions** for the main analysis and suitable **sensitivity analysis** to investigate these assumptions

Sensitivity analysis A series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data.

Sensitivity analysis definition, ICH E9(R1)

- Assumptions made by the analytical approach must be investigated through appropriate **sensitivity analysis**.
- Analyses conducted for reasons other than to investigate the assumptions made by the main analysis are **supplementary analysis**.

⑥ Identify **assumptions** for the main analysis and suitable **sensitivity analysis** to investigate these assumptions

Example – Drug X

Estimand* (slide 28): The difference in means for the change from baseline to Month 6 in SBP between treatment conditions (Drug X regardless of discontinuation and placebo regardless of discontinuation, both in absence of additional medication) in patients with uncontrolled hypertension.

- **Method for estimation* (slide 38):** e.g., assuming all post-treatment discontinuation data were collected, ANCOVA with an appropriate imputation of the measurements after the patient uses additional or alternative medication, based on an adequately justified model.
- **Sensitivity analysis** can explore potential impact of the violations of the model assumption with a tipping point analysis.

⑥ Identify **assumptions** for the main analysis and suitable **sensitivity analysis** to investigate these assumptions

Example – Drug X

- **Consider useful supplementary analysis:**
 - E.g., contrasting the proportion and timing of patients using additional or alternative medication between the treatment groups.
 - Additional supplementary analysis could be planned if helpful for better understanding of the trial data, e.g., based on an analytical approach other than ANCOVA with imputation of the measurements after the patient uses additional or alternative medication.

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⑦ Document the chosen estimands

Estimands should be defined and explicitly specified in the clinical trial protocol

- The choice of estimand will influence the specification of population, variable, aspects of trial design and data collection and the statistical analysis.
- It is therefore recommended that estimands are **specified alongside trial objectives**, even if elucidation of technical aspects is given elsewhere.

⑦ Document the chosen estimands

Estimands should be defined and explicitly specified in the clinical trial protocol

- ICH E9(R1) does not specify the format of the estimand specification.
 - It is required that a reviewer can easily identify intercurrent events and the strategies selected; the population, treatment conditions, variable and population-level summary; and hence a precise estimand description reflecting the scientific question of interest.
- **Estimands for secondary trial objectives that are of key interest should be described fully.** Exploratory objectives can benefit from the same degree of specification, but this is not a requirement.

⑦ Document the chosen estimands

Estimands should be defined and explicitly specified in the clinical trial protocol

- A protocol amendment should be planned if the estimand is to be revised, due to intercurrent events which were **not foreseen at the design stage** and were **identified during the conduct of the trial**, ensuring that alignment with trial design and statistical analysis is maintained.
- If omission of an important intercurrent event is **noted only during the conduct of the trial**, the trial report should discuss not only the way those additional intercurrent events were handled in the analysis but **the effect on what the chosen analysis estimates** and the interpretation of the trial results.

⑦ Document the chosen estimands

Estimands in the clinical trial report

- Results from the main, sensitivity and supplementary analyses should be systematically presented and discussed with **reference to the estimand**.
- Whether each analysis was pre-specified, introduced while the trial was still blinded, or performed post hoc should be reported.
- The **number and timing of occurrence of all intercurrent events** addressed in the estimand should be displayed.
- **Robustness of inferences** should be discussed based on the results from sensitivity analysis.



End of ICH E9(R1) Training material slide decks

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