



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

Training Module 2.1 – Introduction

Addendum to ICH E9 – Statistical Principles for Clinical Trials

ICH E9(R1) Expert Working Group
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International Council for Harmonisation of Technical Requirements
for Registration of Pharmaceuticals for Human Use

Disclaimer

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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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 - A.3.1. Intercurrent Events to be Reflected in the Clinical Question of Interest
 - A.3.2. Strategies for Addressing Intercurrent Events when Defining the Clinical Question of Interest
 - A.3.3. Estimand Attributes
 - A.3.4. Considerations for Constructing an Estimand
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Module 2.5

Outline of Module 2.1

- Understanding treatment effects
- Concerns with current practice that motivate the guidance
- Scope of the addendum to ICH E9
- Examples

Objectives of Module 2.1

- Introduce the **purpose of the addendum**, describing the importance of understanding and accurately quantifying treatment effects.
- Explain concerns with the **misalignment** of trial objectives, design and analysis **in current practice**.
- Introduce the concept of “**intercurrent events**” as events that complicate the description and interpretation of treatment effects. **Examples** are given.
- Introduce a coherent **framework**, including:
 - the introduction of **estimands**;
 - a revised definition for **sensitivity analysis**.



Understanding treatment effects

Understanding treatment effects

- For regulatory approval a medicinal product should have **therapeutic efficacy** and a **positive benefit-risk**.
 - In addition to statistically compelling evidence of efficacy, assessment of benefit-risk considers the **magnitude of the treatment effects**.
- **Treatment effects** are estimated from clinical trials.
- **The treatment effects of interest** should be **specified and agreed before** choices are made **designing a clinical trial** to estimate them.

Understanding treatment effects

- **Treatment effect:** how the outcome of treatment compares to what would have happened to the same subjects under different treatment conditions:
 - e.g., **difference between** treatment A and no treatment;
 - e.g., **difference between** treatment A and treatment B.

Which difference?

- Let's illustrate with a trial in Type II Diabetes Mellitus:
 - If we specify a scientific question of interest as “**the treatment difference between treatment and no treatment on HbA1c at Week 24**” there is still **ambiguity**.

The next slides explain why there is ambiguity

Understanding treatment effects

- Consider a medicine for Type II Diabetes Mellitus.
- What happens **in clinical practice** (and in clinical trials)?
 - Some patients will tolerate a medicine and adhere to its administration schedule, others will not.
 - Some subjects will require changes in dose of concomitant medication or administration of additional medication (e.g., rescue medication, treatment switch, etc.), others will not.
 - ...

In a population or in a clinical trial...



Understanding treatment effects

- Consider a medicine for Type II Diabetes Mellitus.
- What happens **in clinical practice** (and in clinical trials)?
 - Some patients will **tolerate a medicine** and adhere to its administration schedule, others will not.
 - Some subjects will require changes in dose of concomitant medication or administration of additional medication (e.g., rescue medication, treatment switch, etc.), others will not.
 - ...



Some patients will tolerate and adhere to the treatment, others will not... 

Understanding treatment effects

- Consider a medicine for Type II Diabetes Mellitus.
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 - Some patients will tolerate a medicine and adhere to its administration schedule, others will not.
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 - ...



Some patients will require additional medication, others will not...



Different treatment effects can be constructed.

Understanding treatment effects: Multiple definitions of treatment effects

Some patients will tolerate and adhere to the treatment, others will not...



Different measures of effect of treatment on HbA1c at week 24...

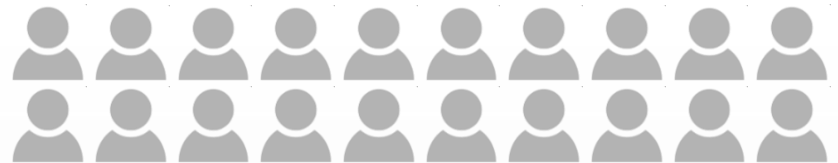
... regardless of **adherence** (i.e. whether the patient is able to remain on treatment).

or

... in the **hypothetical condition** that all patients could **adhere to treatment**.

or

... in the **stratum** of this population that can **adhere to treatment**.



Understanding treatment effects: Multiple definitions of treatment effects

Some patients will require additional medication, others will not...



Different measures of effect of treatment on HbA1c at week 24...

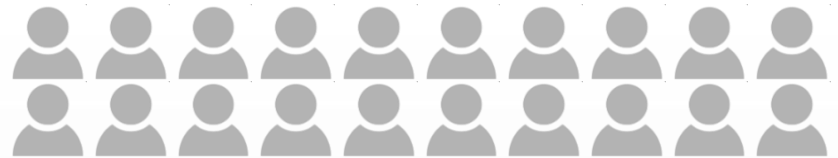
... regardless of whether **additional medication is used**.

or

... in the hypothetical condition that **additional medication was not available**.

or

... in the stratum of this population that does not require **additional medication**.



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Understanding treatment effects



- **Not all alternatives can be reliably estimated.**
- **Not all alternatives will be equally acceptable** for regulatory decision making!

Understanding treatment effects

- Intercurrent events occur after treatment initiation and affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
- Multiple events may need to be considered in the same population, and even for the same subject.



Some patients will tolerate the treatment, others will not...



Some patients will require rescue medication, others will not...



Understanding treatment effects

The **key** point is that **multiple, different treatment effects** can be considered.



- The framework outlined in this addendum gives a basis for describing different treatment effects and some points to consider for the design and analysis of trials to give estimates of treatment effects that are reliable for decision making.

Understanding treatment effects:

Multiple different treatment effects can be considered

What regulatory context is already available on the question of defining treatment effects?

- ICH E9 includes a reference to a **treatment policy** (included in the intention-to-treat principle), but **no alternatives**:

(...) the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment.

Intention-to-treat principle definition, ICH E9 Glossary

Understanding treatment effects:

Multiple different treatment effects can be considered

- Multiple consequences from the **ITT principle** can be distinguished.
 - The trial analysis should **include all subjects** relevant for the research question.
 - Subjects should be included in the analysis **as randomised**.
 - Subjects should be followed up and assessed **regardless of adherence** to the planned course of treatment; those assessments should be **used in the analysis**.

Is that what we want to know for decision making?

- There follows a **case study**, purely for illustrating that:
 - **multiple, different treatment effects can be described**.
 - **problems arise** when the treatment effect of interest is not defined and agreed in advance.

Example: Type II diabetes mellitus

- **Primary endpoint:** Change in HbA1c from baseline to 24 weeks.
- **Applicant:** Estimand not stated
 - **Data collected** after initiation of rescue medication were excluded from the analysis. LOCF used for imputation.
- **Regulator:** Target of estimation and analytical approach considered
 - “While FDA has implicitly endorsed LOCF imputation for diabetes trials in the past, there is now more awareness in the statistical community of the limitations of this approach. *Instead I have included a sensitivity analysis in which the primary HbA1c outcomes are used regardless of rescue treatment, and no statistical adjustment is made for rescue.* This approach is also imperfect, but it comes closer to being a true intent-to-treat (ITT) analysis...”

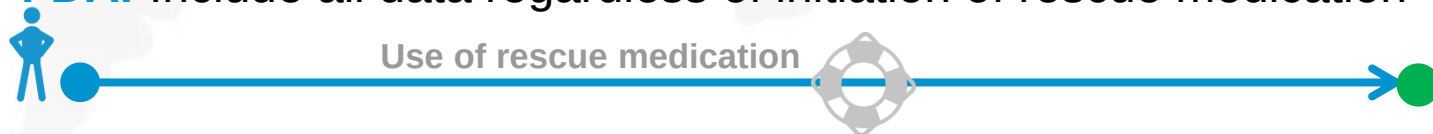
Example: Type II diabetes mellitus

- **Different perspectives on the inclusion of data:**

- **Applicant:** Remove data after initiation of rescue medication, and impute.



- **FDA:** Include all data regardless of initiation of rescue medication



- In this case, absence of an agreed treatment effect of interest led to a primary analysis that was not aligned to the treatment effect of interest preferred by the regulator.
 - **ITT principle ...** *“followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment”* **requires a comparison of treatment policies** ‘dapagliflozin plus rescue’ versus ‘control plus rescue’.

Example: Type II diabetes mellitus

- The applicant had not specified the treatment effect of interest:



It should not be the choices for data collection and data analysis that determine the question of interest!

- The choice of trial design and data collection might have resulted in difficulties for estimation or inadequate statistical power for the analysis, and differences in interpretation of the trial data

This illustrates the importance of reaching agreement over what to estimate: **the estimand**.

Estimand

Estimand A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.

Estimand definition, ICH E9(R1) addendum

Example: Type II diabetes mellitus

- In this case FDA and Applicant use different approaches to deal with the **use of rescue medication**.
 This is an *“intercurrent event”*.
- We can identify two different treatment effects:
 - “to assess the treatment effect **if rescue medication is not available**”;
 - “to assess the treatment effect **regardless of whether rescue medication is used**”.
- These are appropriately thought of as **different questions (estimands)** and not two different answers to the same question.

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) addendum



- These events (e.g., death) that preclude the observation of the variable, should **not be confused** with missing data resulting from **loss to follow-up**!
- **Discontinuation of randomised treatment** represents an intercurrent event whilst **study withdrawal** gives rise to missing data to be addressed in the statistical analysis.

Strategies to address intercurrent events

A “**strategy**” reflects the choice made on **how to address intercurrent events**, in order to describe the **treatment effect** that is targeted.

- The addendum introduces **five strategies** that can be used alone or in combination to **address different intercurrent events**.
 - Treatment policy
 - Hypothetical
 - Composite
 - While on treatment
 - Principal stratum



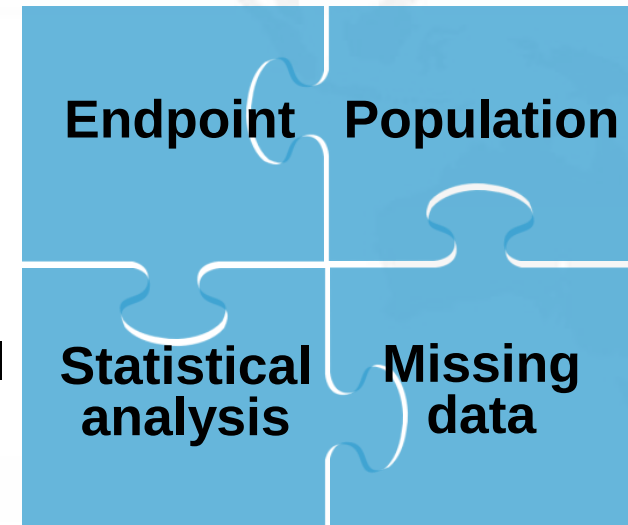
Concerns with current practice

Concerns with current practice



Currently:

- Targets of estimation that are not clearly stated and cannot necessarily be inferred from information in the study protocol and statistical analysis plan.
- Choices are made for data handling and statistical analysis that are not consistent with the treatment effect of interest



- **Practice should be reversed:**

- The **target of estimation** should be clear from the **study protocol**;
- The **statistical analysis** should be **aligned to the agreed target of estimation**.

Concerns with current practice



Use of the Intention-to-treat principle:

- ITT is mentioned in protocols, statistical analysis plans and trial reports, but **only** as a way of specifying which patients are included in the analysis set, and not to reflect the principle that patients will be followed-up regardless of “their compliance to the planned course of treatment”.

Lack of clarity exists in the majority of clinical trials over **which treatment effect is being estimated**: if it is not aligned to the ITT principle and treatment policy, then what?

- Estimating something other than an effect aligned to the ITT principle might be acceptable, but the alternative must be **precisely specified** and **agreed**.

Concerns with current practice



Missing Data

- In addition to study discontinuations, patients who discontinue the assigned treatment, start another treatment, or die are all **treated generically as “missing data”** causing problems for analysis and inference.
- Some methods for handling of “missing data” in current practice **mis-represent treatment effects** that are nevertheless used in drug licensing decisions and reported to prescribers.
 - E.g., modelling to address the exclusion of data for patients who discontinue treatment, based on those patients who do not, when estimating a treatment effect aligned to the ITT principle.

Concerns with current practice

Targets of estimation

- The precise targets of estimation are **not always easily identifiable** from study reports, and the reported “treatment effect” can be **misunderstood**.
- Targets of estimation, once identified, might **not be relevant to decision makers** (e.g., regulators, HTA bodies, payers, prescribers and patients).

External validity

- There are concerns that clinical trials are less representative if the sponsor tries to avoid the occurrence of, or the impact of, intercurrent events that will occur in clinical practice, e.g., patients discontinuing from treatment or using additional medications.

Concerns with current practice



Sensitivity analysis

- Analyses currently labelled as “sensitivity analyses” can in fact have **different targets of estimation** (estimands), so that consistent results between analyses should not necessarily be expected.
- Requirements that a **broad range of sensitivity analyses** all give consistent results might **unnecessarily** increase the hurdle for demonstration of therapeutic efficacy.

Concerns with current practice



Analysis sets

- Trials often include repeated measurements on the same subject and the Full Analysis Set is incorrectly specified.
 - ICH E9 strongly recommends that analysis of superiority trials be based on the full analysis set, but elimination of planned measurements on some subjects can have similar consequences to excluding subjects altogether from the analysis.
- Per-protocol analysis is subject to severe bias: can the need to explore the impact of protocol violations and deviations be addressed in a way that is less biased and more interpretable than naïve analysis of the per-protocol set?
- The treatment effect of interest should be defined in a way that determines the population of subjects to be included in the estimation **and the observations from each subject to be included in the analysis considering the occurrence of intercurrent events.**

Concerns with current practice

Bad drugs might appear good and good drugs might appear bad!

- **Bad drugs might appear good:**
 - Consider a drug for a chronic condition for which efficacy and toxicity are related.
 - Patients who benefit can also experience toxicity.
 - In a trial some patients exposed to the drug will benefit no more than patients exposed to placebo; others will benefit but **need to discontinue from treatment due to toxicity**.
 - Even if no-one benefits in the long term, it can be imagined that choices made on which data to collect and include, and the analytical approach, can either **create** or **exaggerate** a positive treatment effect.

Concerns with current practice

Bad drugs might appear good and good drugs might appear bad! [illustration continued]

- **Good drugs might appear bad:**
 - Consider a placebo-controlled trial testing a medicine that is, in fact, effective, where patients can use rescue medication when experiencing inadequate response.
 - Imagine that use of rescue occurs markedly more on placebo than on experimental treatment and that rescue medication is also effective.
 - A treatment effect defined “regardless of whether **additional medication is used**” and estimated accordingly, is likely to be **lower** than the effect of treatment “in the hypothetical condition that **additional medication** was not available” or “in the strata of this population that do not require **additional medication**” ([see Slide 16](#)).

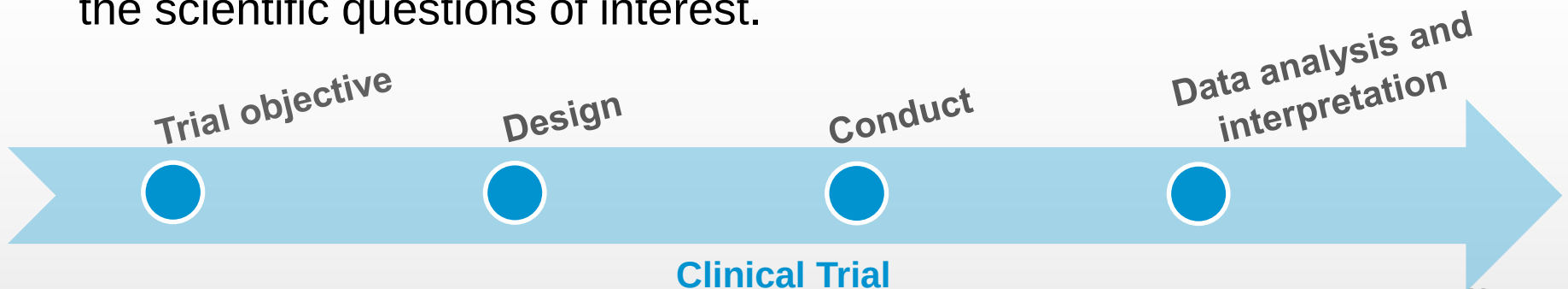


Scope of the addendum to ICH E9

Framework

A framework and language are introduced to:

- Promote **alignment between trial objectives, design, conduct, analysis and inference**;
- Promote understanding that trial objectives cannot be translated into estimands without reflecting how potential **intercurrent events** are addressed in the scientific question of interest;
- Promote discussion of different **strategies** to handle **intercurrent events** in order to identify and describe the treatment effects that reflect the scientific questions of interest.



Framework

A framework and language are introduced to:

- Define a treatment effect of interest - **before a trial is designed and conducted** - that is relevant to use of a medicine in clinical practice;
- Highlight the importance of considering whether a main analysis will derive an estimate which is reliable for inference and for regulatory decision making;
- Re-define **missing data**;
- Re-define **sensitivity analysis** and the regulatory assessment of robustness;
- Introduce **supplementary analysis** as any other analysis conducted to fully investigate and understand the trial data.

Opportunities

Aligning drug developers and regulatory bodies' expectations for the target treatment effect in advance has the potential to give:

- More **meaningful descriptions of treatment effects** for licensing and prescribing decisions; ✓
- Clinical trials with designs that are **aligned to agreed objectives**; ✓
- **Increased transparency** with respect to data analysis and inference; ✓
- More **predictable** regulatory assessment **procedures**. ✓

Scope

- The ICH E9(R1) addendum **builds on ICH E9**:
 - its primary focus is **confirmatory clinical trials**;
 - **clarity on treatment effects** of interest for regulatory **decision making** is demanded.
- However, the framework is applicable whenever treatment effects are to be estimated and tested:
 - whether related to **efficacy** or **safety**;
 - the main focus is on **randomised clinical trials** but the principles are also applicable for **single arm trials** and **observational studies**;
 - **any data type** (e.g., longitudinal, time-to-first event, recurrent event)
 - in **other phases of clinical development**, including post-authorisation;
 - regardless of **therapeutic area** or **experimental design**.



Examples

The need for defining
estimands

Example 1: End of life in cancer patients

- **Context:**
 - For end of life cancer patients, medicines might be developed and administered to maintain weight, functioning and quality of life for the duration of the patient's remaining life.
- **Measures of efficacy:**
 - Body weight, body composition (DEXA), hand-grip strength and QoL assessment scales.
- **Intercurrent event:**
 - A non-negligible proportion of patients will die, which needs to be considered in defining the treatment effect of interest.

Example 1: End of life in cancer patients

- This is based on a **real example** where,
 - without statement of the estimand (treatment effect of interest) deaths were handled as **missing data** and outcomes imputed / modelled according to the analysis plan;
 - **interpretation** of trial results was **difficult**;
 - estimates of effect calculated on that basis had **questionable relevance** to effects in **clinical practice**;
 - trying to identify an outcome at Week 12 for the statistical analysis, for the patients who had previously died, was arguably **meaningless**.
- What treatment effect should be of interest considering that some patients will die within 12 weeks of initiating treatment?

Example 2: Cardiovascular safety

- **Context:**

- In some chronic conditions (e.g., diabetes) current practice is to conduct **large outcome trials** to exclude large harmful effects on **cardiovascular safety**, with the **potential to demonstrate a beneficial effect**.
- E.g., patients are randomised to a treatment vs. placebo on top of a background regimen that might differ between patients.

- **Measures of efficacy:**

- Patients are followed to observe MACE (major adverse cardiovascular events), often over a period of years.

Example 2: Cardiovascular safety

- **Intercurrent events:**

- Patients **discontinue assigned treatment, initiate new treatment and change background treatment**. Analyses can be conducted, largely in line with the ITT principle (i.e., subjects are followed up, assessed and analysed irrespective of their compliance to the planned course of treatment) in respect of these “intercurrent events”.

- **Estimand:**

(E.g.,) Difference between treatment and placebo in incidence of MACE regardless of whether patients discontinue assigned treatment, initiate new treatment or change background treatment.

- Will this provide an estimate of a treatment effect that is **relevant** to understanding the **cardiovascular risk of the treatment**?
- Are there **better strategies** for addressing these “intercurrent events” that give **greater insights into the safety profile of the treatment**?

Next module:

2.2. Framework

**Implications on design and conduct of
clinical trials and in the performance of
statistical analyses**