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

Training Module 1: Summary

Addendum to ICH E9 – Statistical Principles for Clinical Trials

ICH E9(R1) Expert Working Group
December 2021

International Council for Harmonisation of Technical Requirements
for Registration of Pharmaceuticals for Human Use

Disclaimer

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

The presentation does not represent official guidance or policy of authorities or industry and it does not provide additional guidance beyond ICH E9(R1).

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Introduction note

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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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Summary

The addendum aims to improve the planning, design, analysis and interpretation of clinical trials.

- Clear trial objectives should be translated into key clinical questions of interest by defining suitable **estimands**.
- An **estimand** (i.e. “what is to be estimated”) is 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.

Check Module 2.1

Summary

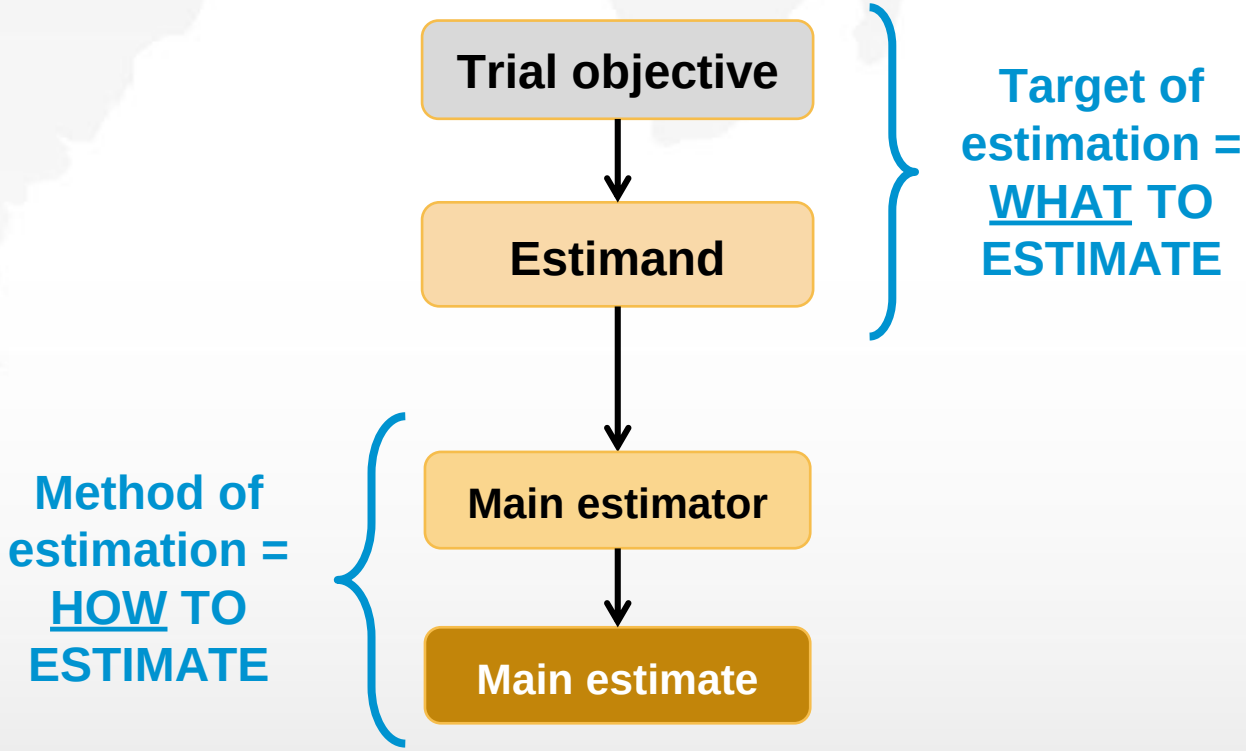
The addendum aims to improve the planning, design, analysis and interpretation of clinical trials.

- **Without** a precise description of the trial objective and the treatment effect that is targeted for testing and estimation there is a risk that:
  - the study **will not be designed appropriately** to address its objective;
  - the statistical analyses will be **misaligned** to the trial objective and the target of estimation;
  - the treatment effect that is reported will be **incorrectly interpreted,** which risks **misleading** decision makers.

This is important for all researchers and healthcare professionals designing, conducting, or interpreting a clinical trial

Summary

This addendum presents a structured framework to link trial objectives to a suitable trial design and tools for estimation and hypothesis testing.



Summary

- Having clarity in the trial objectives when describing the treatment effect of interest at the planning stage should **inform appropriate choices** about trial design, data collection and statistical analysis.
- The addendum aims to facilitate dialogue regarding the treatment effects that a clinical trial seek to estimate:
  - **between disciplines** (clinician, statistician, etc);
  - **between sponsor and regulator**.

Check Module 2.3

Summary

- The description of an estimand will not be complete without reflecting how potential **intercurrent events** are addressed in the clinical question of interest.
- **Intercurrent events** are events occurring after treatment initiation and affect either the interpretation or the existence of the measurements associated with the clinical question of interest, e.g.:
  - use of an alternative treatment, perhaps a rescue medication;
  - discontinuation of treatment;
  - terminal events such as death.
- Missing values due to e.g. study withdrawal or loss-to-follow-up are **not intercurrent events** and are not to be reflected in the estimand, but instead represent limitations to the data that need to be addressed in the statistical analysis.

Check Module 2.3

Summary

- Different **strategies** are introduced to address potential **intercurrent events** reflecting the clinical question of interest.
- The **choice of strategy** for each intercurrent event should be the subject of **multi-disciplinary discussion** between, e.g. clinicians and statisticians, and discussion between sponsor and regulator.
- Disease under study, clinical context (e.g. availability of other treatments), administration of treatment, and goal of treatment will influence the choice of strategies. The experimental situation should also be considered as it may differ to that which is anticipated in clinical practice.
- **Different strategies** will often be used to reflect the clinical question of interest in respect of **different intercurrent events**.

Check Module 2.4

Summary

- Having specified an **estimand** (= WHAT TO ESTIMATE), the addendum addresses **impact on trial design**, **conduct** and **analysis** (= HOW TO ESTIMATE).
- In respect of estimation, the addendum calls for greater precision on what is labelled as **'missing data'**. Specifically, having clarity in the estimand and the methods for estimation gives a basis for planning **which data need to be collected** and hence which data, when not collected, present a missing data problem to be addressed.

Check Module 2.5

Summary

- The addendum gives a more precise focus to requirements for **sensitivity analysis**.
- With an agreed estimand, and a pre-specified statistical analysis that is aligned to that estimand, sensitivity analysis can focus on **sensitivity to deviations from assumptions** in respect of a particular analysis, rather than sensitivity to the choice of analytic approach.
- **Supplementary analysis** for an estimand can also be planned in order to more fully investigate the trial data and understand the treatment effect, **complementing** the main and sensitivity analyses.

Check Module 2.6

Summary

- The addendum calls for changes in **trial documentation**.
- Estimands should be defined and **explicitly specified in the clinical trial protocol**.
- The protocol and the statistical analysis plan should pre-specify the **main estimator for each estimand**, together with a suitable **sensitivity analysis** to explore the robustness under deviations from its assumptions.
- While the primary estimand will be the main drive for the study design, estimands for **secondary trial objectives** that are likely to support regulatory decisions should also be defined and specified explicitly.

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Next module:

2.1. Introduction

Understanding treatment effects and motivation for the ICH E9(R1) addendum. Scope of the document and examples.

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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**.

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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

HbA1c: Glycated haemoglobin

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.
- What happens **in clinical practice** (and in clinical trials)?
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  - …

Some patients will require additional medication, others will not…

Different treatment effects can be constructed.

Check addendum section A.3.2!

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**.

Check addendum section A.3.2!

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**.

Back to Slide 37

Check addendum section A.3.4!

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.

ITT: Intention-to-treat

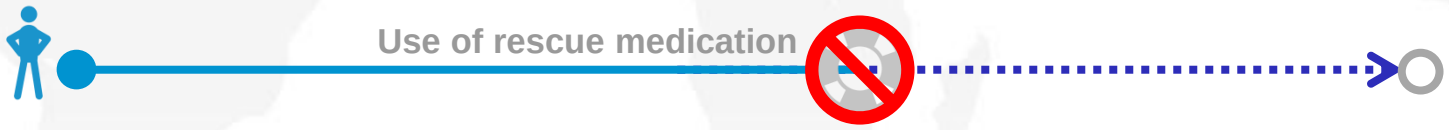
Example: Type II diabetes mellitus

- **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..."

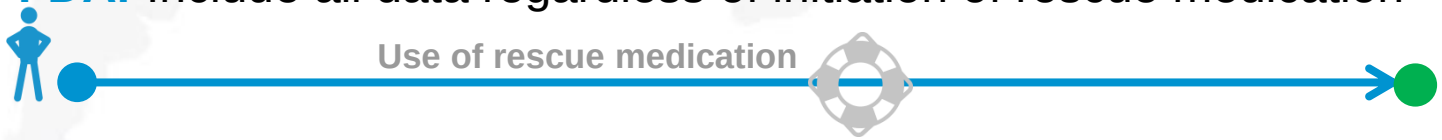
HbA1c: Glycated haemoglobin
LOCF: Last observation carried forward

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'.

ITT: Intention-to-treat

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.

Check addendum section A.3.2!

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

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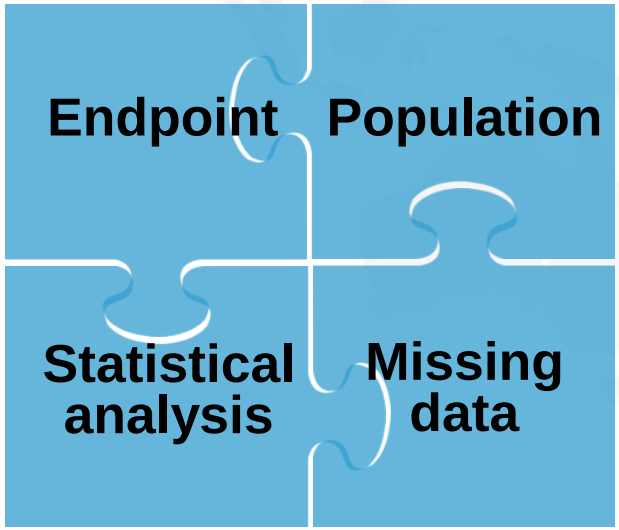
Concerns with current practice

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**.

ITT: Intention-to-treat

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.

ITT: Intention-to-treat

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.

HTA: Health technology assessment

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).

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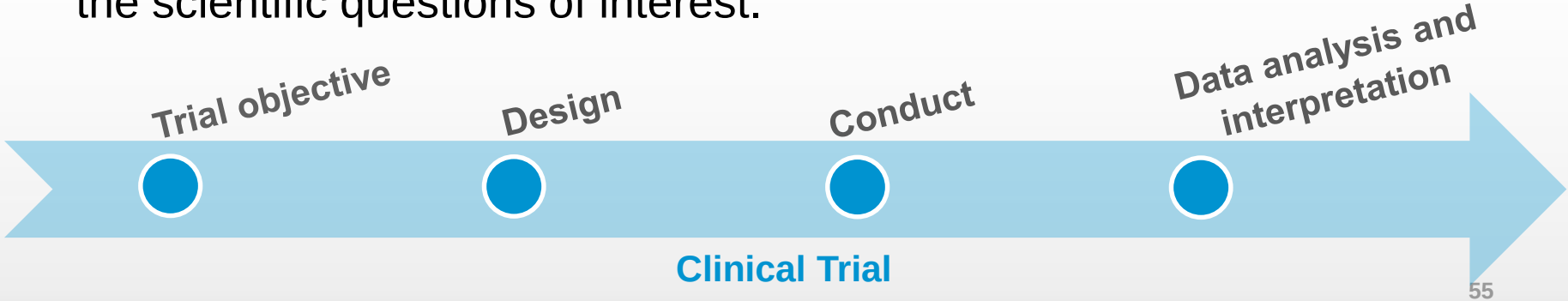
Scope of the addendum to ICH E9

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**.

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Examples

The need for defining estimands

Check Module 3: Generic example

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.

DEXA: Dual-energy X-ray absorptiometry
QoL: Quality of life

Check Module 3: Generic example

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**?

ITT: Intention-to-treat
MACE: Major adverse cardiac events

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Next module:

2.2. Framework

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

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Training Module 2.2 – Framework

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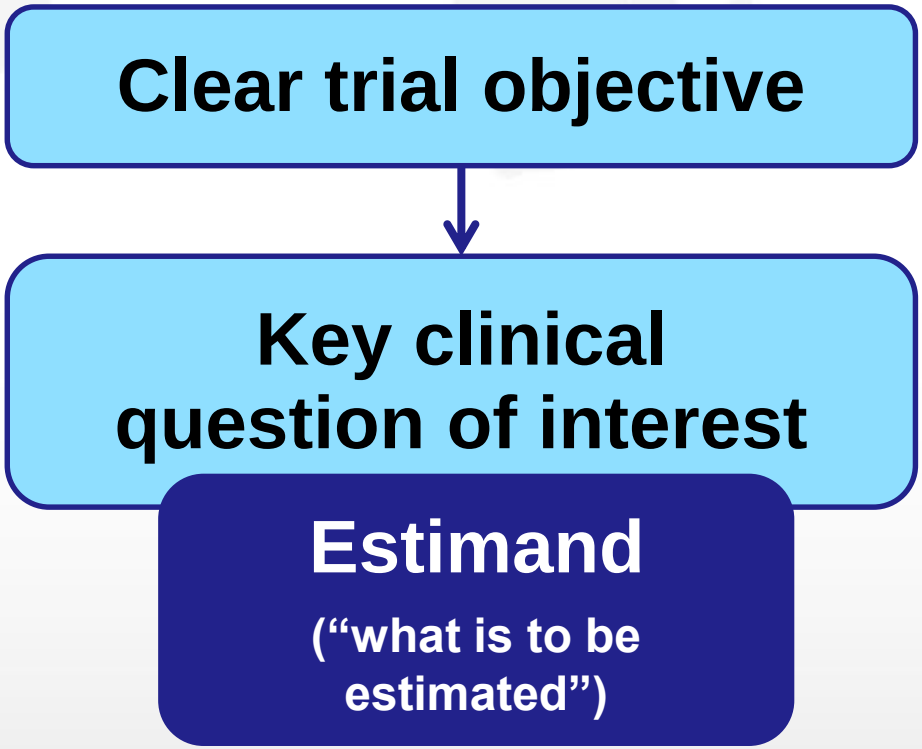
Outline of Module 2.2

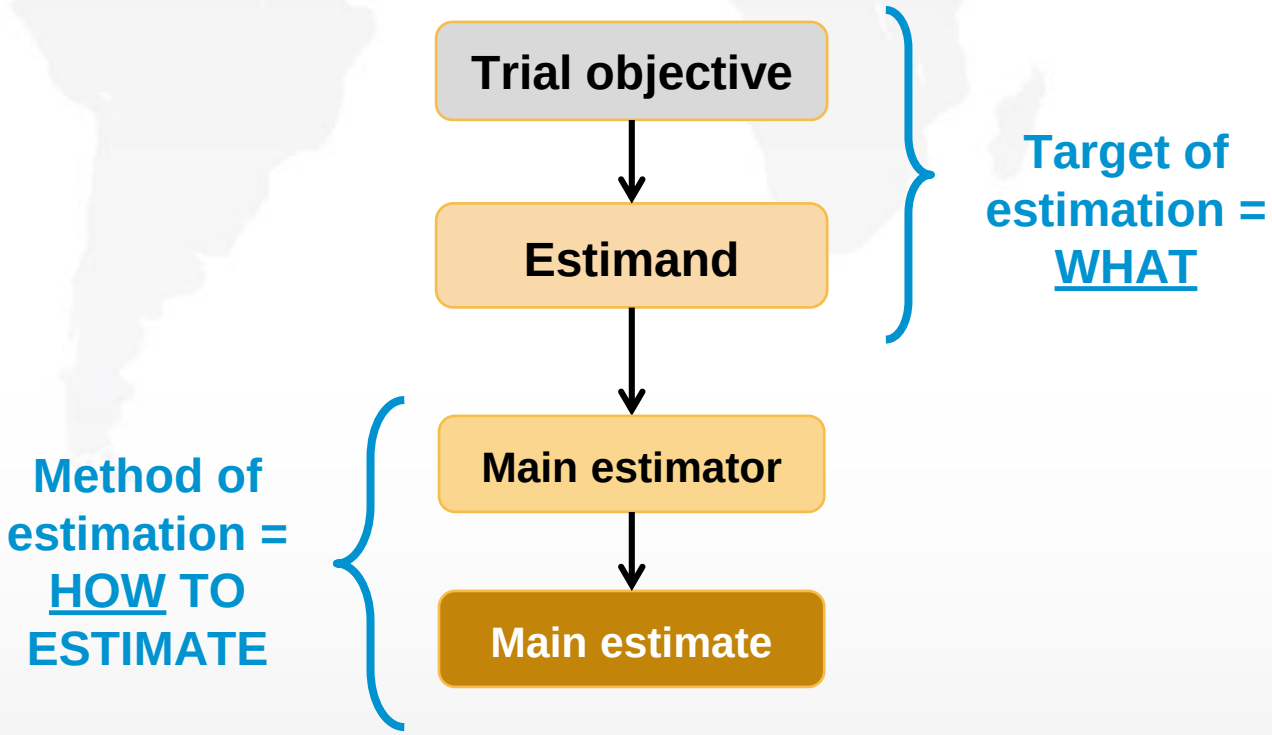
- A new framework for clinical trials
- Alignment between trial objective, design, planning, conduct, analysis and interpretation
- How this framework can improve discussions between sponsors and regulators on the suitability of designs and the interpretation of results

A "new" framework

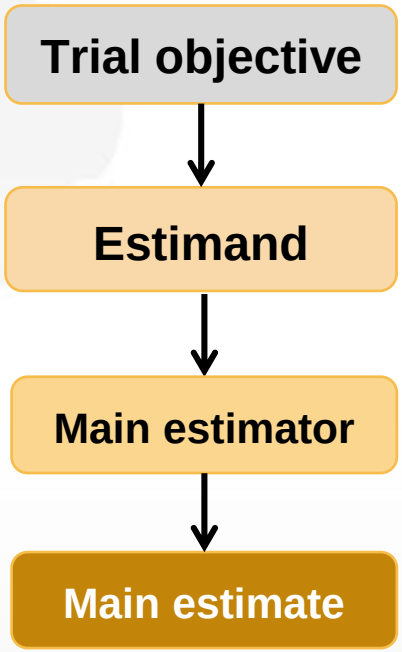
Clear trial objectives should be translated into key clinical questions of interest by defining suitable estimands.



Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective



Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

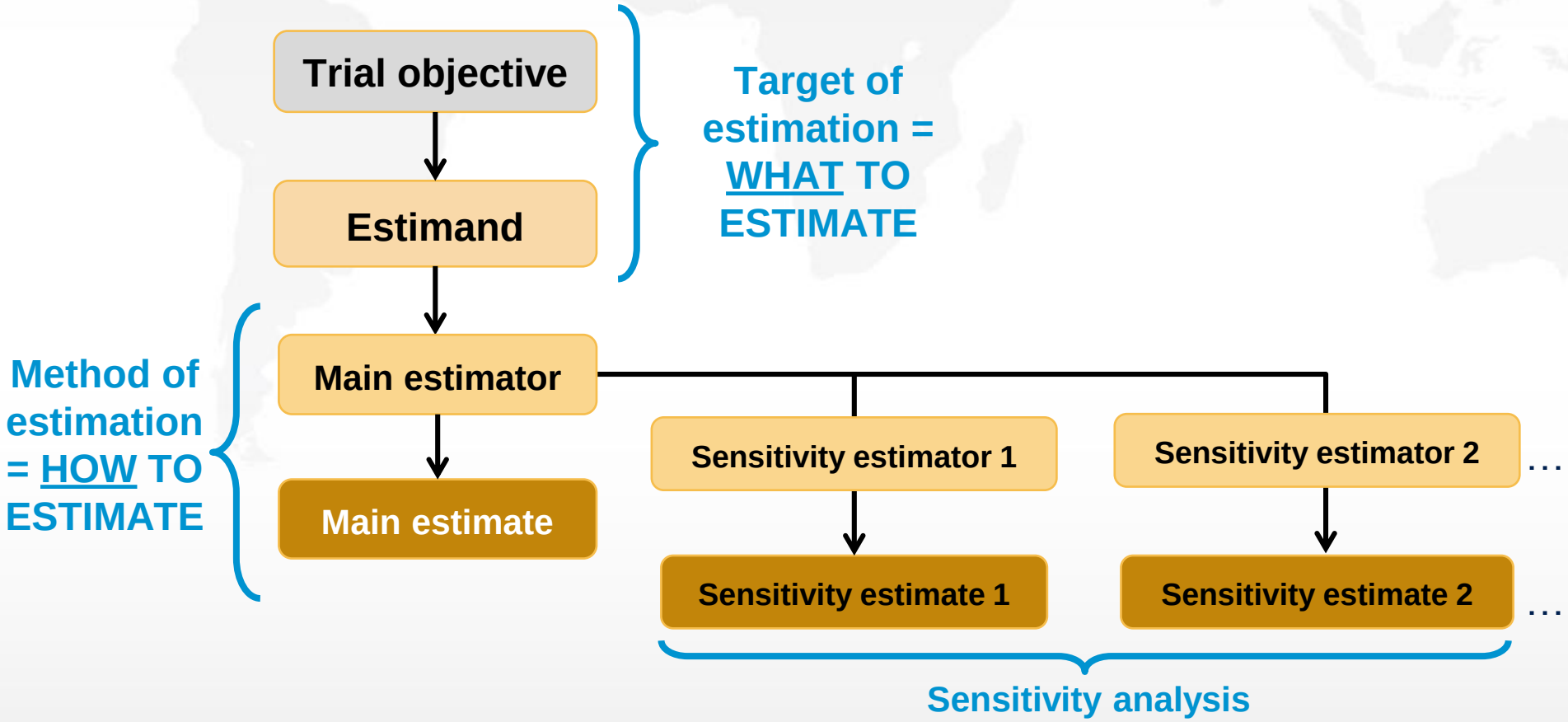


Target of estimation = WHAT TO ESTIMATE

Method of estimation = HOW TO ESTIMATE

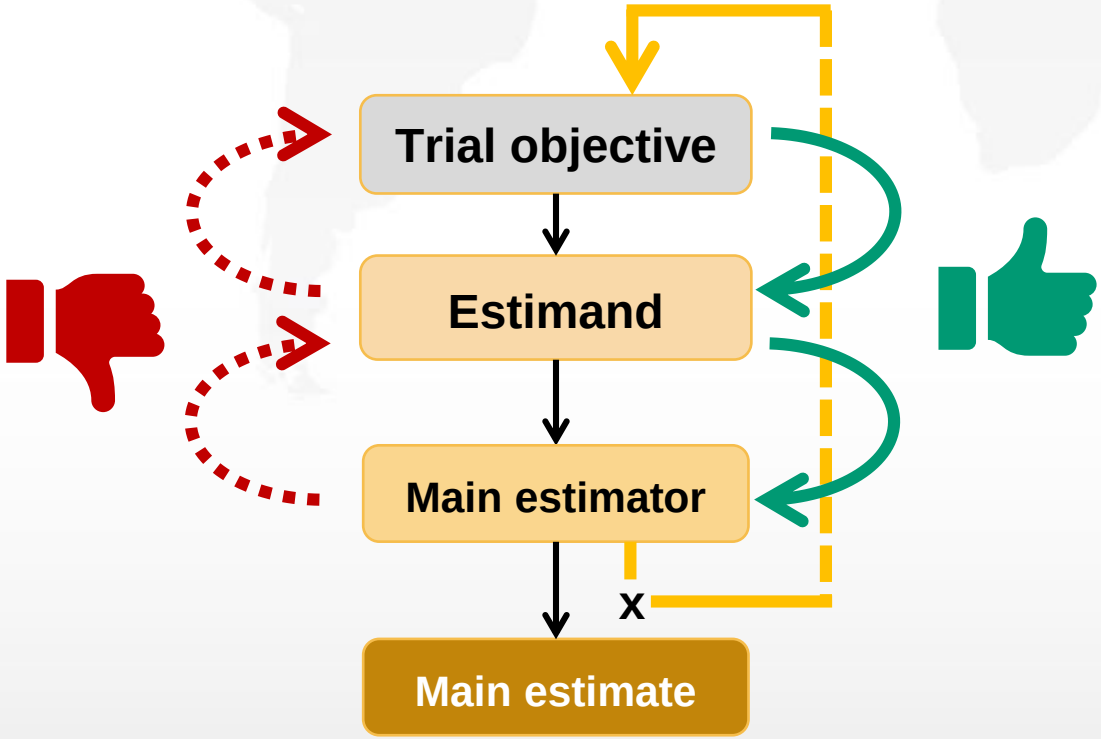
- The **main estimator** will be underpinned by certain **assumptions**.
- To explore the **robustness** of inferences from the main estimator to deviations from its underlying assumptions, **sensitivity analysis** should be conducted, in form of one or more analyses, **targeting the same estimand**.

Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective



Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

Trial planning should proceed sequentially. The trial objective should determine the choice of estimands and the estimands should determine the choice of estimators, not the reverse.



The trial objectives need to be defined first and inform top-down the choice of estimand and estimator (**green** arrows). The main estimator should never define the trial objective from bottom-up (**red** arrows). Where significant issues exist to derive a reliable estimate (x) for a particular estimand, the trial objectives need to be re-considered, and the process should restart from the top (**yellow** arrow).

A new framework

Appropriate estimands will be the main determinant for aspects of trial design, conduct and analysis.

A new framework

A common language and common understanding of this framework will help **sponsors planning trials** and **regulators in their reviews**, enhancing the **interactions** between these parties when discussing the suitability of designs, and the interpretation of results, to support drug licensing.

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Next module:

2.3. Estimands

Description, strategies and construction of estimands

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

Training Module 2.3: Estimands

Addendum to ICH E9 – Statistical Principles for Clinical Trials

ICH E9(R1) Expert Working Group
December 2021

International Council for Harmonisation of Technical Requirements
for Registration of Pharmaceuticals for Human Use

Disclaimer

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

The presentation does not represent official guidance or policy of authorities or industry and it does not provide additional guidance beyond ICH E9(R1).

Legal Notice

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

ICH E9(R1) – Table of Contents

Outline of Module 2.3

- Intercurrent events need to be considered in relation with the clinical question of interest
- Five strategies are suggested for addressing intercurrent events
- Five attributes used to construct an estimand
- Considerations for constructing estimands

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Module 2.3

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

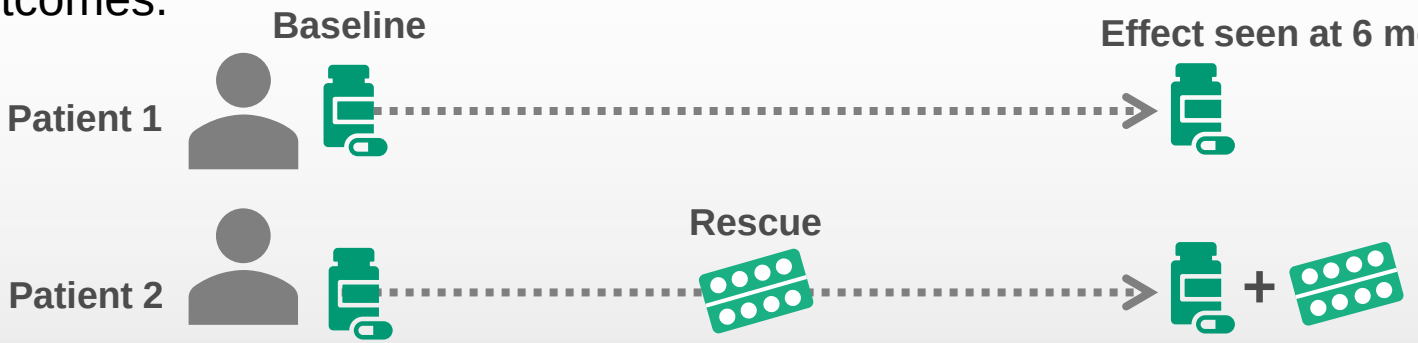
Quantification of treatment effect

A central question for drug development and licensing...

How does the outcome of a treatment compares to what would have happened to the same subjects under different treatment conditions?

e.g. had they not received the treatment or had they received a different treatment.

- **Intercurrent events** need to be considered.
  - The occurrence of intercurrent events may depend on treatment conditions (e.g. had patients not received the treatment or had they received a different treatment) which can impact data collected to assess clinical outcomes.



Quantification of treatment effect

A central question for drug development and licensing...

How does the outcome of a treatment compares to what would have happened to the same subjects under different treatment conditions?

e.g. had they not received the treatment or had they received a different treatment.

- **An estimand defines in detail what needs to be estimated to address a specific scientific question of interest, posed by the trial objective.**
  - It summarises at a population level what the outcome would be in the same patients under different treatment conditions being compared.
  - 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.

Description of an Estimand

- Before the trial starts → **define the targets of estimation → design the trial** to allow reliable estimation of the targeted treatment effect.
- The description of an estimand involves **precise specifications of certain attributes**
  - The attributes should be developed based on **clinical considerations** and on **how intercurrent events should be addressed** (in line with the clinical question of interest)
- The Addendum introduces **strategies** to describe the question of interest in respect of intercurrent events.

It is critically important to understand the differences between the strategies and to **clearly indicate which are used in constructing the estimand**.

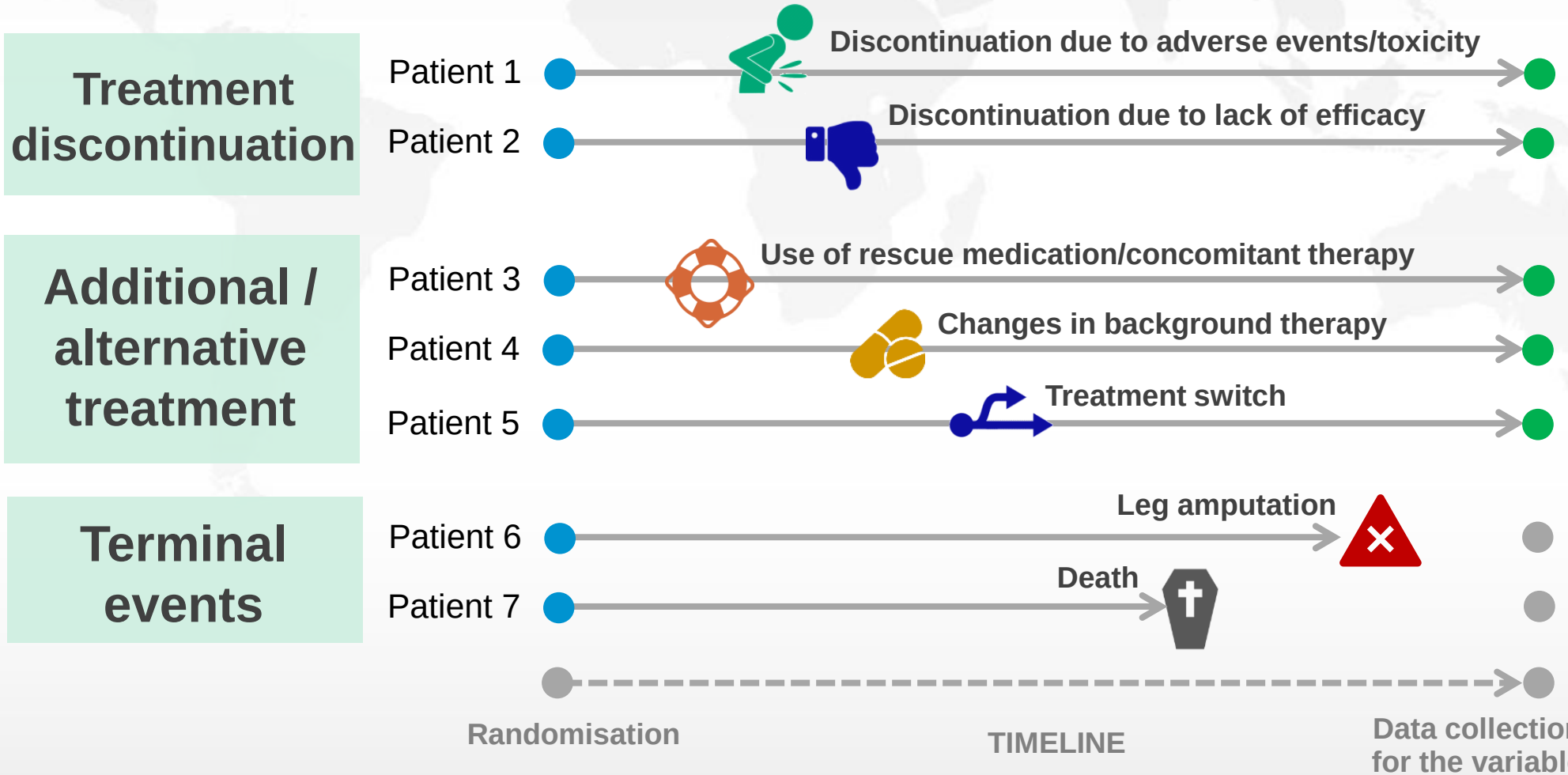
Intercurrent events

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

Unlike missing data, intercurrent events are not to be thought of as a drawback to be avoided in clinical trials, as they can also occur in clinical practice!

Intercurrent events - examples



See Principal stratum strategies - slide 33

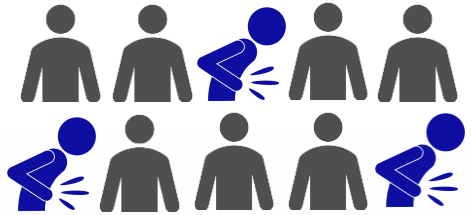
Intercurrent events - examples

- Some **clinical events** can also be **intercurrent events** when their **occurrence (or non-occurrence) defines a principal stratum** of interest.
- Examples may include:

Tumour shrinkage
(= objective response)

… when assessing a treatment effect on duration of response in oncology

Occurrence of infection



… when assessing a treatment effect on severity of infections occurring after vaccination of initially uninfected subjects

Need for precision when describing IEs

- An intercurrent event might be identified solely by the event itself, such as discontinuation of treatment, or might be **more granular** (e.g. including the reason - discontinuation due to toxicity).
- It may be necessary to establish the **magnitude or degree of the event.** For example, rescue medication to be considered an intercurrent event if more than a certain amount is taken, for more than a certain period of time, or in a specific timing (e.g. after week 20).
  - Additional treatment may be given in different conditions (e.g. replacing or supplementing an ineffective/toxic treatment, a temporary add-on, etc) – these may need to be considered (and described) separately.
- The **need for precision** is particularly important when **different strategies are to be used** depending on the specific conditions of the intercurrent event.

Intercurrent events ≠ missing data

- Intercurrent events are **not a missing data problem**. IEs are considered and the estimand is defined before the trial is designed.
- Study withdrawal, loss-to-follow-up and other reasons for missing data (such as administrative censoring in survival studies) are not generally regarded as intercurrent events.

> **Missing data** Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.
>
> *Missing data definition, ICH E9(R1) addendum*

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Module 2.3

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

Strategies for addressing intercurrent events

- The following slides will describe possible strategies to address 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!

How are potential intercurrent events reflected in the scientific question of interest?

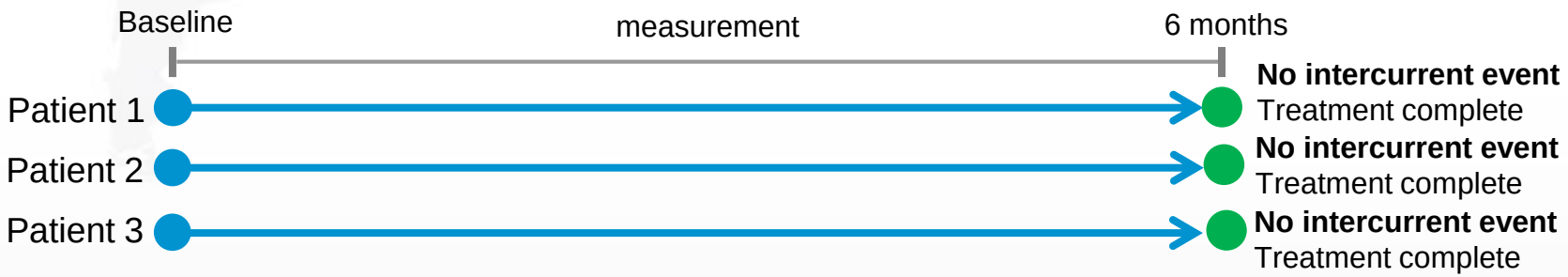
Let's take an example…

Drug X → Indicated for a chronic, non-life-threatening disease

- **Response to treatment:** monitored monthly **(continuous measurement)**.
- **Main clinical question: comparison of Drug X to placebo at month 6 →** best addressed by a randomised controlled trial.
- **Considerations on intercurrent events:**
  - Use of **placebo** in the clinical trial is considered ethical but only if provision is made for subjects to **discontinue their treatment and use rescue medication** due to **lack of efficacy** (after which it is still possible to collect data for the variable).
  - It is also possible to collect data after other intercurrent events such as **discontinuation of treatment due to an adverse event**, but not for intercurrent events such as death (considered very unlikely in this setting).

If we assume that no intercurrent events occur – (unrealistic) example

- **Estimand:** Difference in means between treatment conditions in the change from baseline to month 6 in the designated measurement in the targeted patient population.
- Let's consider **three patients** and what could happen if no intercurrent events occurred (this slide), and under each strategy (following slides).



Legend:

- 6-month value has been collected
- Part of patient time course considered

Now assuming that there are intercurrent events…

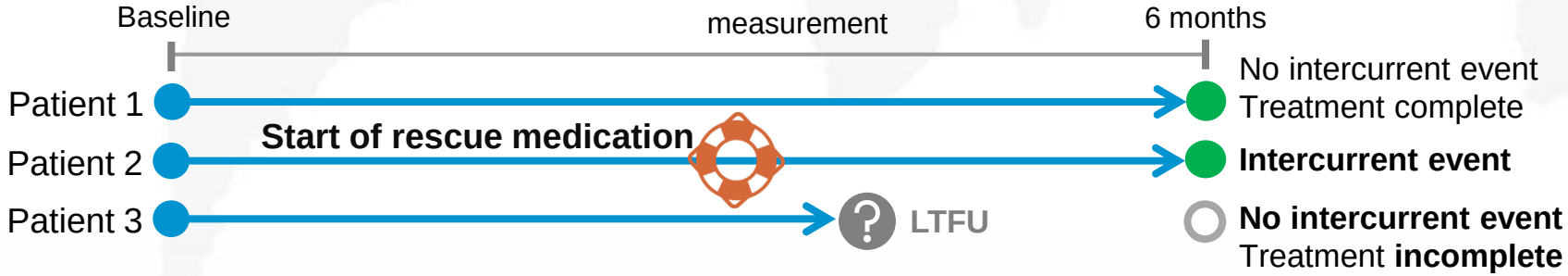
See treatment attribute – slide 44

1. Treatment policy strategy

- In this strategy, the occurrence of the intercurrent event is **irrelevant** in defining the treatment effect of interest:
  - The data collected for the variable of interest are used **regardless of whether or not the intercurrent event occurs.**
- For example, when specifying how to address rescue medication as an intercurrent event, occurrence of the intercurrent event is ignored (disregarded) and the observations collected after use of rescue medication for the variable of interest are used.
- The **intercurrent event is** considered to be **part of the treatments** being compared, reflecting the Intention-to-treat (ITT) principle defined in ICH E9.
- In general, this strategy **cannot be implemented for terminal intercurrent events** since values for the variable after the intercurrent event **do not exist**.
  - For example, an estimand based on this strategy cannot be constructed with respect to a variable that cannot be measured due to death.

1. Treatment policy strategy - example

- **Estimand:** Difference in means between treatment conditions in the change from baseline to month 6 in the targeted patient population, regardless of whether rescue medication was used.
- **If rescue medication (intercurrent event) is used…**



- **Applying the treatment policy strategy**

Legend:

- 6-month value has been collected
- 6-month value has not been collected, data are missing
- LTFU - Patient lost to follow-up
- Intercurrent event - in grey when disregarded
- Part of patient time course considered
- Part of patient time course not observed and needs to be imputed/predicted

See treatment attribute – slide 44

2. Hypothetical strategies

- In these strategies, a hypothetical scenario is envisaged in which the intercurrent event would not occur.
  - For example, when rescue medication must be made available for ethical reasons, a treatment effect of interest might concern the outcomes **if rescue medication had not been available.**
- The value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined.
  - In this example, the value to be considered would have been the one collected **if patients had not had rescue medication available**.
  - By definition, such value cannot be observed but may need to be implicitly or explicitly **predicted / imputed**.

See treatment attribute – slide 44

2. Hypothetical strategies

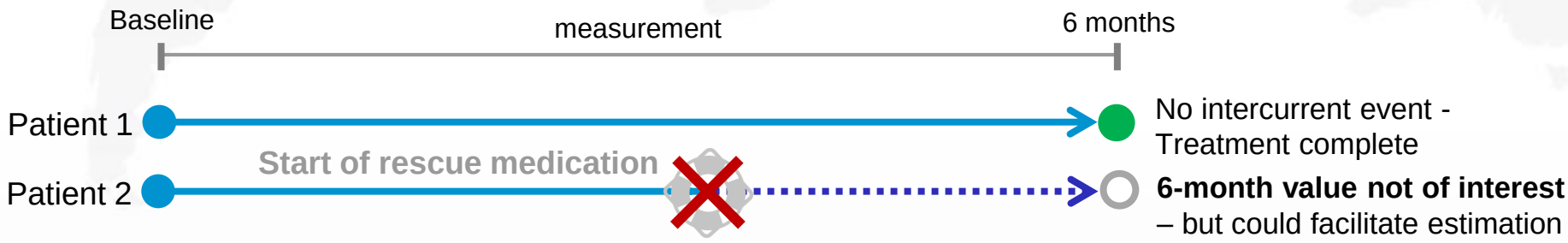
Important to keep in mind…

- **Many potential hypothetical scenarios** can be envisaged, but not all will be **interesting for regulatory decision making.**
  - For example, it may be of relevance to consider the effect of a treatment under **different conditions from those of the trial that can be carried out** (like rescue medication not being available).
- The hypothetical scenario **should consider reasonable situations**, e.g. a scenario where a toxic medicine is considered to be non-toxic is <u>not</u> usually relevant for decision making.
- It has to be **clear what hypothetical scenario** is envisaged and **why it is clinically relevant**. E.g. wording such as “if the patient does not take additional medication” can be confusing – it may be because it is not available, or the particular patient is supposed not to require it.

2. Hypothetical strategies - example

- The **estimand** assesses the difference in means between treatment conditions in the change from baseline to month 6 in the targeted patient population, in an alternative, hypothetical setting where rescue medication was not available to patients.

- **Applying a hypothetical strategy**



Legend:

- 6-month value has been collected and outcome is positive
- No need to collect 6-month value
- Part of patient time course considered
- Part of patient time course not observed, may need to be imputed/predicted
- Intercurrent event hypothetically not present. Time of intercurrent event marks the end of data collection unless it facilitates estimation.

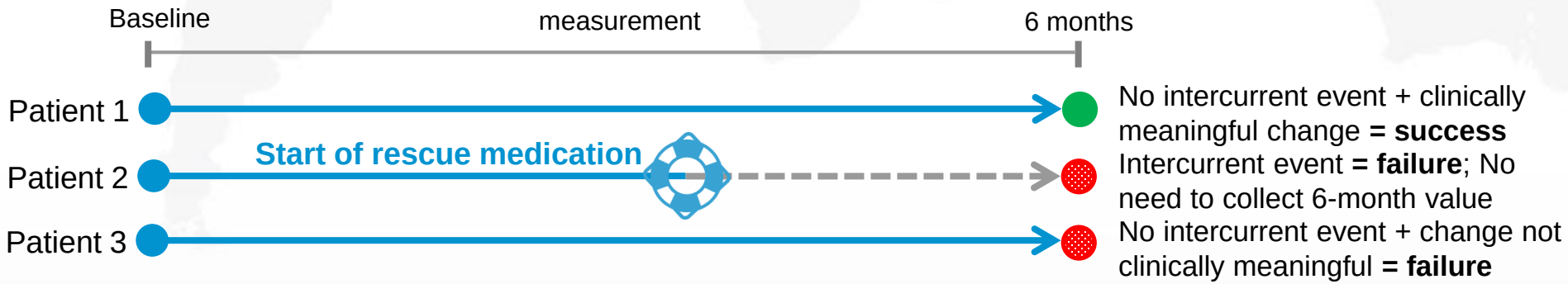
See variable attribute – slide 46

3. Composite strategies

- The composite strategies relate to the variable of interest.
- The **occurrence of the intercurrent event is informative** about the effect of the treatment and so it is **incorporated in the endpoint**.
  - For example, if a patient takes rescue medication it may be considered that the allocated treatment was not effective, and the patient was not successfully treated. If the outcome is already success/failure, use of rescue would dictate treatment failure.
- Composite strategies **do not need to be limited to dichotomous endpoints**, e.g. if outcomes are measured in a scale or score, subjects who experience the intercurrent event could be given a bad value.
- Composite strategies are particularly useful for handling **terminal events** (such as death). They can also be very useful secondary estimands.

3. Composite strategies - example

- The **estimand** assesses the treatment effect based on a clinically meaningful change in the designated measurement in patients who do not take rescue medication.
- **Applying a composite strategy (on a categorical scale)**



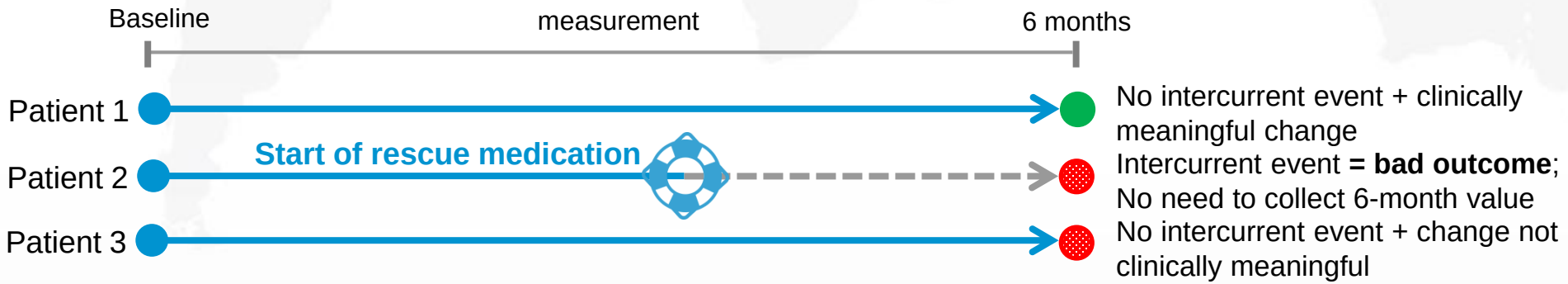
- This is **not the only way** to address intercurrent events using the composite strategy; other ways include trimmed means or quantiles (see next slide).

Legend:

- 6-month value has been collected and outcome is positive
- Outcome is negative regardless of having been collected
- Part of patient time course considered
- Part of patient time course not considered.
- Intercurrent event as part of the composite variable. Time of intercurrent event marks the end of data collection.

3. Composite strategies - example (cont'd)

- The **estimand** assesses the treatment effect based on a clinically meaningful change in the designated measurement in patients who do not take rescue medication.
- **Applying a composite strategy (on a continuous scale)**



Legend:

- 6-month value has been collected and outcome is positive
- Outcome is negative regardless of having been collected
- Part of patient time course considered
- Part of patient time course not considered.
- Intercurrent event as part of the composite variable. Time of intercurrent event marks the end of data collection.

See variable attribute – slide 46

4. While on treatment strategies

- For these strategies, response to treatment **prior to the occurrence of the intercurrent event** is of interest.
  - This could be, for example, the last measurement before death (or other intercurrent event) or at a pre-defined time-point, whichever comes first.
  - If a variable is measured repeatedly, its values up to the time of the intercurrent event may be considered to account for the intercurrent event, rather than the value at the same fixed time point for all subjects.
  - **For example:**
    - subjects with a terminal illness may discontinue a palliative treatment because they die, yet it is relevant to measure the success of the treatment based on the effect on symptoms before death (if death is unrelated to the effect of the treatment).

See variable attribute – slide 46

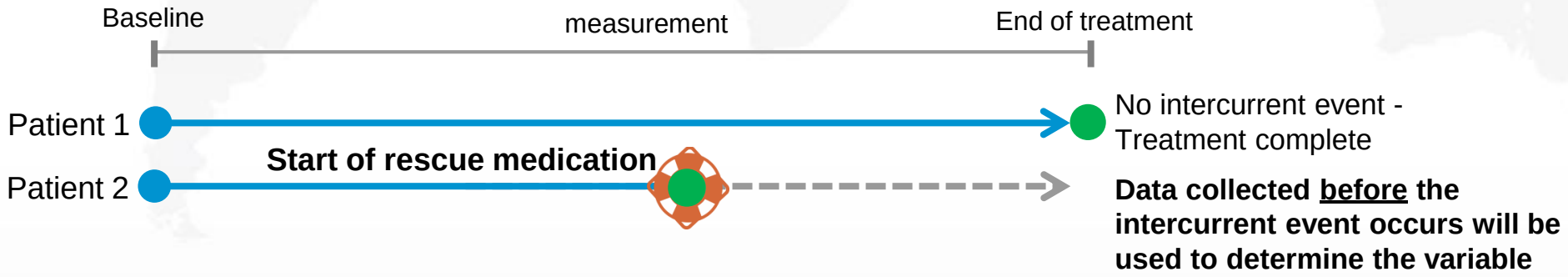
4. While on treatment strategies

- **For example (cont.):**
  - subjects might discontinue treatment, and in some circumstances it will be of interest to assess the risk of an adverse drug reaction during the period of adherence to treatment.

- The while on treatment strategies can **impact on the definition of the endpoint**, for example, by restricting the observation time of interest to the period between baseline and the occurrence of the intercurrent event.
- The terminology used in the strategy will depend on the intercurrent event of interest: e.g. “while on treatment”, “while alive”, etc.
- Particular care is required if the occurrence of the intercurrent event **differs between the treatments being compared**

4. While on treatment strategies - example

- The **estimand** assesses the treatment effect on the variable measurement. The variable chosen here addresses the outcomes while being on treatment, i.e., before start of rescue medication.
- **Applying a while on treatment strategy**



Difficulties arise in deriving an estimate that is reliable for inference when follow-up times are different between groups.

Legend:

- End point value has been collected
- Part of patient time course considered
- Part of patient time course not considered
- Time of intercurrent event marks end of data collection (merged with green dot).

See population attribute – slide 45

5. Principal stratum strategies

- These strategies relate to the population of interest to address the clinical question of interest.
- The clinical question of interest relates to the treatment effect **only within a principal stratum**, composed by the target population (subset of the broader population) in which the intercurrent event would (or would not) occur.
  - For example, we may want to know the effect of a treatment on severity of infections in the principal stratum of patients becoming infected after vaccination.
  - Or in the treatment effect among the patients who can tolerate a toxic test treatment.

See population attribute – slide 45

5. Principal stratum strategies

- Effects in a principal stratum, which is based on potential intercurrent events (e.g. patients who would not discontinue treatment if assigned to the test product, regardless of them actually being assigned to it or not) should be clearly distinguished from any type of subgroup or per-protocol analyses where membership is based on the trial data (i.e. subjects who do not discontinue the test treatment when assigned to it).
  - Subjects who experience an intercurrent event on the test treatment will often be a different subset from those who experience the same intercurrent event on the control.
- It is **not possible in general to identify these subjects** directly, either
  - in advance of the trial since the occurrence of the intercurrent event cannot be perfectly predicted, or
  - based on the data from a parallel-group randomised controlled trial because each patient will be observed on one treatment only.

5. Principal stratum strategies - example

- A given patient can receive either treatment or placebo.
- When receiving treatment some patients will require rescue medication, others not. The same applies for patients on placebo.
- The **estimand** can assess, for example, the treatment effect in the stratum of patients which would not use rescue medication regardless to which treatment arm they would be assigned → corresponding to stratum S11 (see below).

Patients fall into exactly one of these four strata:

- S_{00}: stratum of patients who require rescue medication independently of treatment or placebo;
- S_{01}: stratum of patients who require rescue medication on placebo and do not require it on treatment;
- S_{10}: stratum of patients who require rescue medication on treatment and do not require it on placebo;
- S_{11}: stratum of patients who do not require rescue medication independently of treatment or placebo. This is the only stratum where the intercurrent event of use of rescue medication does not occur.

		Treatment: Rescue medication	Treatment: No rescue medication
Placebo	Rescue medication	S_{00}	S_{01}
Placebo	No rescue medication	S_{10}	S_{11}

A population can be defined by membership of one or more of these strata.

Multiple intercurrent events – example

- The strategies presented before can be used **alone or in combination** to address **multiple different intercurrent events**.

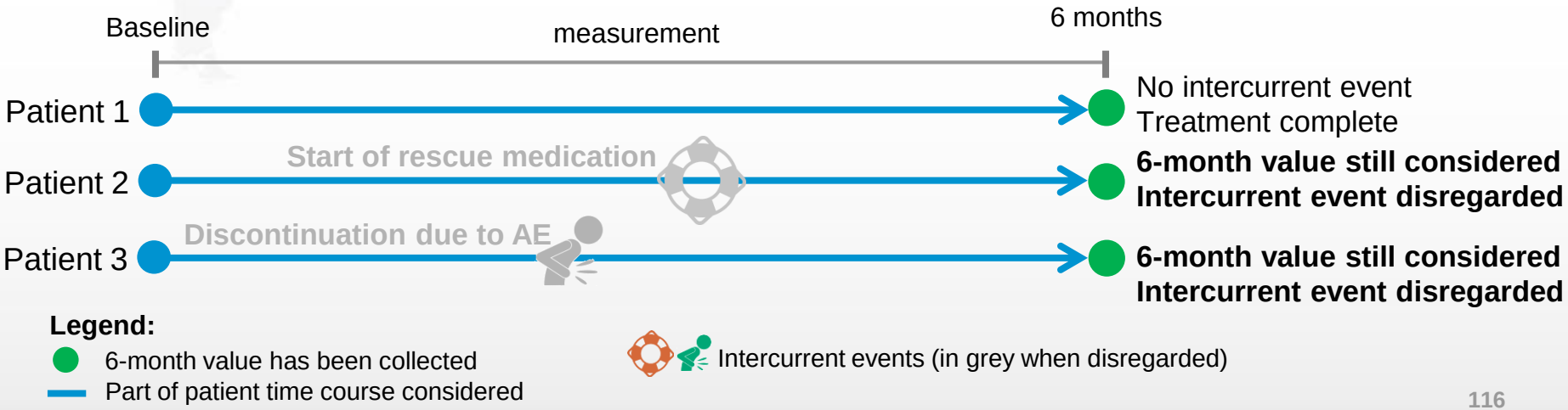
Returning to the example:

- **Drug X**, indicated for the treatment of a chronic, non-life-threatening disease.
- **Response to treatment:** monitored monthly (continuous measurement).
- **Main scientific question:** comparison of drug X to placebo at month 6.
- **Intercurrent events:**
  - Use of **placebo** in the clinical trial is considered ethical but only if provision is made for subjects to discontinue their treatment and **use rescue medication** due to lack of efficacy (after which it is still possible to collect data for the variable).
  - This is also the case after other intercurrent events such as **discontinuation of treatment due to an adverse event**, but not for intercurrent events such as death (considered very unlikely in this setting).

Second intercurrent event

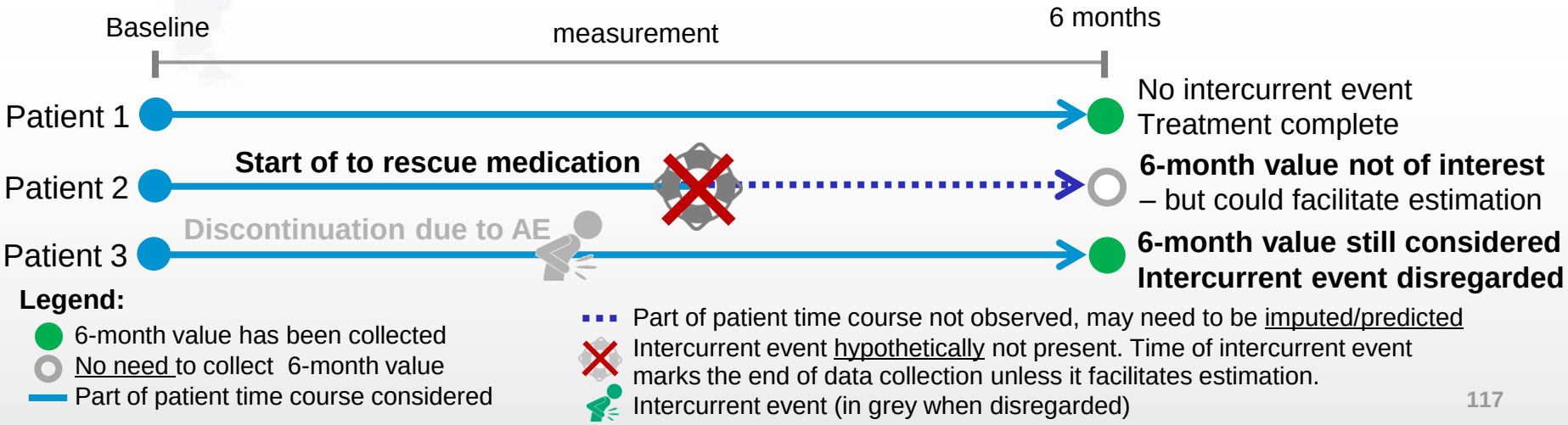
Multiple intercurrent events – example

- **Treatment-policy strategy to account for both intercurrent events:**
- **Estimand:** Difference in means between treatment conditions in the change from baseline to month 6 in the targeted patient population, regardless of whether or not rescue medication had been used and regardless of treatment discontinuation due any adverse events.
- **Applying treatment-policy x treatment-policy strategy…**



Multiple intercurrent events – example

- **Combination of hypothetical strategy and treatment-policy strategy to account for the two intercurrent events:**
- **Estimand:** Difference in means between treatment conditions in the change from baseline to month 6 in the targeted patient population had rescue medication not been made available to subjects prior to month six and regardless of study treatment discontinuation due to an adverse event.
- **Applying hypothetical x treatment-policy strategy…**



Further considerations on strategies

The choice of strategies must be the object of a **multidisciplinary discussion** in particular, between **sponsors and regulators**.

The description of the preferred strategy for handling **each intercurrent event** should be **precisely defined in the study protocol**, as well as the **reasons** for that choice.

The strategies' names are just for ease of reference its use is not mandatory.

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Module 2.3

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

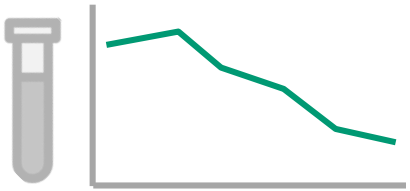
Estimand attributes

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

Treatment

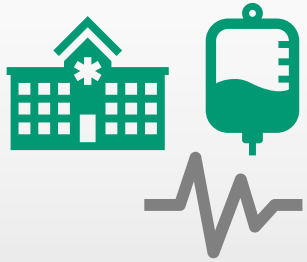
Population

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

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

IE: Intercurrent event

Treatment

The treatment condition of interest, and treatment to be compared

*May include alternative treatments and how these are handled – **policy**, hypothetical*

Population

Patients targeted by the clinical question

Can be defined by a

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

All these attributes can be combined to describe the

estimand

intercurrent events

Any other IEs that have not yet been reflected in the specification of treatment, population or variable

summary for the variable

Provides a basis for comparison between treatment conditions

IE: Intercurrent event

See Treatment policy strategy – slide 22

Estimand attributes

Treatment

The treatment condition of interest, and treatment to be compared

*May include additional treatments and how these are handled – **Treatment policy, hypothetical***

Treatment condition of interest and alternative treatment to which a comparison will be made

- These may include:
  - Individual interventions (e.g. test drug, medical device, health intervention, etc.)
  - Combinations of interventions administered concomitantly (e.g. as add-on to standard of care, or a regiment including a sequence of interventions
  - Allowed rescue treatments and changes in background medications
- If variations to the specified treatments are to be considered **intercurrent events**, this should be clearly **specified in this attribute** (e.g. use of rescue, changes in background treatments).

See Principal stratum strategies – slide 33

Estimand attributes

Population

Patients targeted by the clinical question

Can be defined by a ***principal stratum***

Treatment condition of interest and alternative treatment to which a comparison will be made

- This will be represented by:
  - The **whole trial population**, **or**
  - A **subgroup** defined by a particular characteristic measured at baseline, **or**
  - A **principal stratum** (or strata) defined by the occurrence (or non-occurrence) of an intercurrent event

See Composite & WoT strategies – slides 27 & 30

Estimand attributes

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***

Variable (or endpoint) to be obtained for each patients in order to address the clinical question of interest

- The specification of the variable may include whether the patient experiences an **intercurrent event** – such as when composite or while on treatment strategies are used. For example:
  - using composites (e.g., treatment failure defined as non-response or treatment discontinuation), or
  - using measurements taken prior to discontinuation of treatment (e.g. occurrence of an adverse drug reaction while exposed to treatment).

IE: Intercurrent event

Estimand attributes

Other intercurrent events

Any other intercurrent event that have not yet been reflected in the specification of treatment, population or variable

- Intercurrent events are likely accounted for
  - …as part of the treatment of interest or alternative treatment (treatment policy strategy, hypothetical strategy);
  - …as part of the population (principal stratification strategy);
  - …as part of the variable (composite strategy, while on treatment strategy).
- **If not yet addressed in the previous attributes**, other intercurrent events and the strategies to address them should be specified in this attribute
  - Any other intercurrent event will usually be reflected using treatment policy, hypothetical or while on treatment strategies.

Estimand attributes

Population-level summary for the variable

Provides a basis for comparison between treatment conditions.

Population-level summary for the variable

- It could be, for example, a mean or a proportion or, possibly, a hazard rate.
- In case of treatment comparisons, examples are:
  - the difference in mean change from baseline to one year in HbA1c, or
  - the difference or ratio in the proportion of subjects meeting specified criteria, under two different treatment conditions.
  - a hazard ratio, t-year event-rate difference or restricted mean survival time difference.

HbA1c: Glycated haemoglobin

Study objectives

Clinical question of interest with clear study objectives

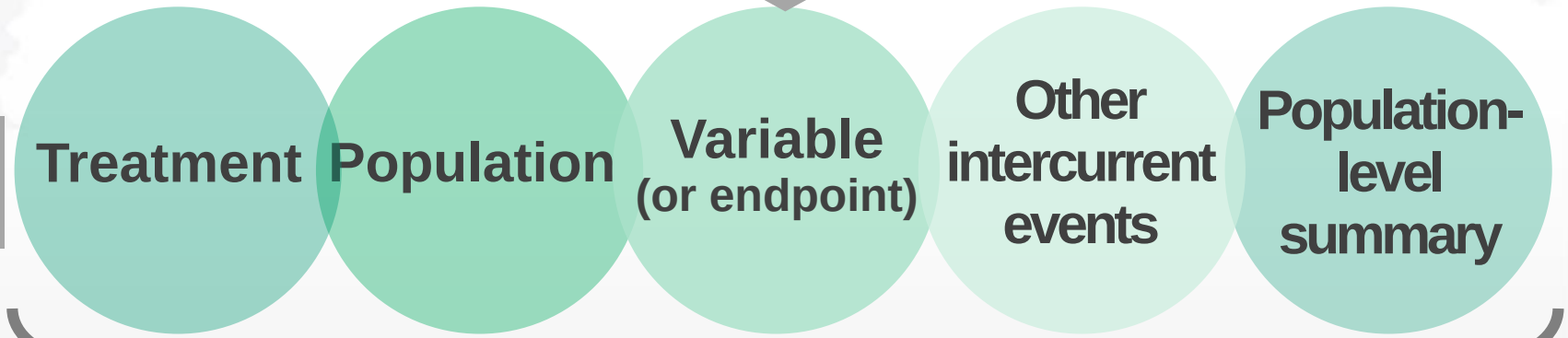
Intercurrent events

Treatment discontinuation, use of additional or alternative treatment, terminal events, etc.

Strategies

Treatment policy | Hypothetical | Composite | While on treatment | Principal stratum | Other

Attributes



ESTIMAND

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Module 2.3

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

Considering intercurrent events

Define **trial objectives** considering the impact of IEs such as treatment discontinuation, use of additional treatments, terminal events, etc.

Need to consider:

- **Clinical relevance** for the specific therapeutic setting
- Clear understanding of the **treatment**
- **Experimental situation**
- Deriving a **reliable estimate** for decision making

Clear and unambiguous definition of the target of estimation = estimand

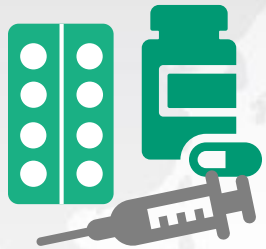
Construction of an estimand

Clinical relevance in the therapeutic setting

The construction of the estimand should consider **what is of clinical relevance** for the particular treatment in the particular therapeutic setting.

Considerations include:

- Disease under study;
- Clinical context (e.g. if there are alternative treatments available, first in class…);
- Administration of the treatment (e.g. one-off, short-dosing, chronic dosing…);
- Goal of the treatment (e.g. prevention, disease modification, symptom control…).



Construction of an estimand

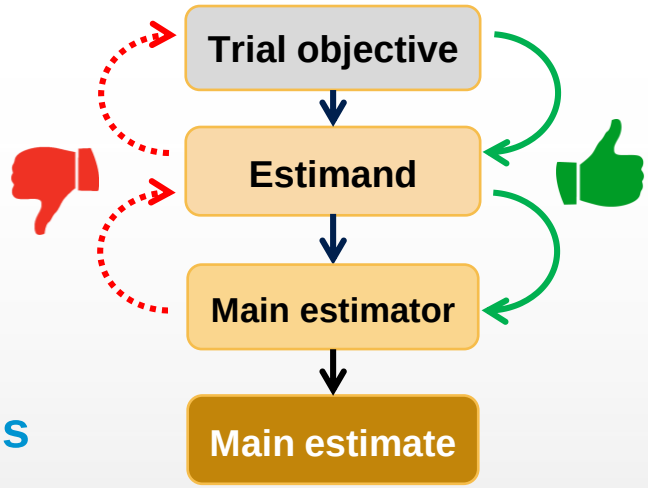
Clear understanding of the treatment

- When constructing the estimand it is necessary to have a **clear understanding of the treatment** to which the clinical question of interest pertains.
- A clear specification of the treatment allows to clarify what **additional treatments could be seen as intercurrent events (or not);**
  - This includes **background treatments, concomitant medications, use of later-line therapies, treatment switching and conditioning regimens**, etc.
  - For example, if the use of a certain amount of concomitant steroids is allowed in the intervention, this needs to be clear in the definition of the treatment *(e.g. treatment A with concomitant use of steroids up to X mg per week)*, otherwise any use of steroids could be considered an intercurrent event and would need to be handled in the definition of the estimand.
- Some intercurrent events will need to be reflected in the **population** and **variable attributes**, depending on the strategies selected.

Construction of an estimand

Deriving a reliable estimate for decision making

- It is also important to guarantee that an **estimate of the treatment effect** can be derived that is **reliable for decision making**.
- Depending on the chosen strategies, **values after the occurrence of intercurrent events may or may not be relevant for estimation**.
- It should be agreed that a **reliable estimate is possible to obtain before the choice of estimand is finalised** – this includes also the existence of appropriate methods to estimate (replace) values that are no longer relevant after the intercurrent event, and are not to be used in the analysis.
- Some estimands may require **more assumptions** than others



Avoiding or over-simplifying this process risks misalignment between trial objectives, trial design, data collection and statistical analysis!

- If it is **not possible to obtain a reliable estimate** for a certain preferred estimand, **different strategies may need to be chosen**.
- Nevertheless, it is important to **proceed sequentially from the trial objective** and an understanding of the clinical question of interest, and **not** for the choice of data collection and method of analysis to determine the estimand.
- However, sometimes it is **not possible to foresee every relevant intercurrent event** at the planning stage. **Trial reporting** should then discuss not only the way unforeseen intercurrent events **were handled in the analysis** but also **the effect on what the revised analysis estimates**.

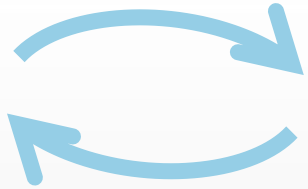
Construction of an estimand

The construction of estimands is a **multi-disciplinary undertaking** and should be the subject of discussion between sponsors and regulators.

Sponsors

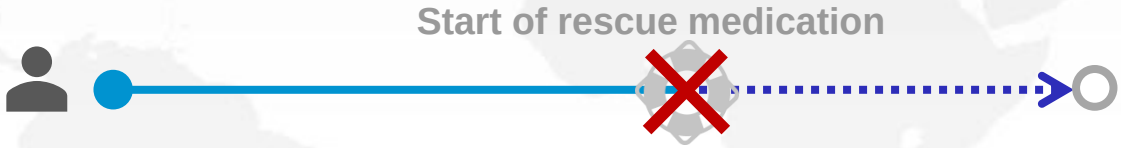
Trial design and conduct

Trial objectives, estimands and design



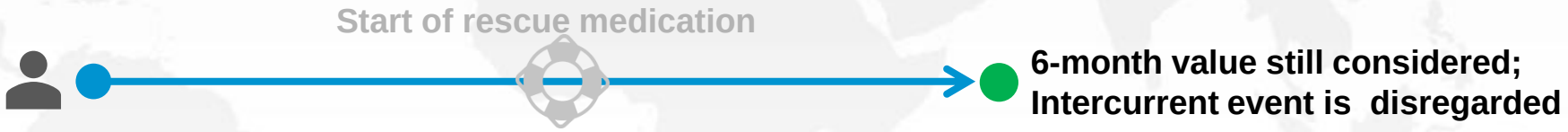
Regulators

Notes about the hypothetical strategy



- Some hypothetical conditions are **likely to be more acceptable to regulatory decision making** than others, for example:
  - Treatment effect had rescue medication not been available → Relevant question
  - Treatment effect had patients who discontinued treatment due to adverse events not been able to tolerate it → Not a relevant question
  - Treatment effect had all patients been able to complete the treatment → Not enough detail
- The **hypothetical conditions** described must therefore be justified for the quantification of an **interpretable treatment effect** that is **relevant to inform regulatory decisions and the use of the medicine in clinical practice**.

Notes about the treatment policy strategy



- Treatment policy strategies might be **more generally acceptable to support regulatory decision making.**
- Also in settings where:
  - Estimands based on other strategies might be considered of greater clinical interest, but no other estimators can support a reliable estimate or robust inference.
- The treatment policy strategy might offer the possibility to obtain a reliable estimate of a **treatment effect that is still relevant**.
  - The resulting estimates should be presented along with a discussion of the limitations, in terms of trial design, data collection or statistical analysis
- **Inference can be complemented** by additional estimand and analysis pertaining to each intercurrent event for which the strategy is used – this is applicable to all strategies.

Estimands for non-inferiority and equivalence trials

- Considerations for **constructing estimand in a NI or equivalence scenario** may **differ from those for superiority** comparisons, since the problem facing the regulator in their decision making is different.
  - In NI and equivalence trials the **use of a treatment policy strategy** (which would correspond to analysing using the full-analysis set under the ITT principle described in ICH E9) is generally **not conservative**, since responses in both treatment groups **can appear more similar after intercurrent events** such as treatment discontinuation or use of rescue medication.
- Estimands can be constructed to **directly address** the intercurrent events that could **artificially lead to attenuation of differences.**
- It should be noted, though, that trials aiming to **detect differences between treatments** (e.g. biosimilars, generics) are likely to require **different estimands** from those aiming to **quantify evidence efficacy** (more often NI).
  - Estimands can be constructed to prioritise sensitivity to detect differences, if important for regulatory decision making.

NI: Non-inferiority
ITT: Intention-to-treat

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Next module:

2.4. Impact on trial design and conduct

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

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

Training Module 2.4: Impact on trial design and conduct

Addendum to ICH E9 – Statistical Principles for Clinical Trials

ICH E9(R1) Expert Working Group
December 2021

International Council for Harmonisation of Technical Requirements
for Registration of Pharmaceuticals for Human Use

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- 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

ICH E9(R1) – Table of Contents

Outline of Module 2.4

- ICH E9(R1) will have implications on how we design and conduct clinical trials and perform statistical analyses
- Identification of estimand(s) at the design stage requires informed discussion with all stakeholders
- Certain estimands may require or benefit from non-standard designs and/or endpoints

Impact on Trial Design

- The **design of a trial** needs to be **aligned to the estimands** that reflect the **trial objectives**.
- **ICH E6** lists important aspects of **trial design** that should be stated in the **protocol**. **Alignment with the trial objective and estimand** should be sought when considering, for example:
  - The type of trial (e.g., double-blind, placebo-controlled, parallel design);
  - Duration of subject participation, discontinuation criteria for individual subjects, subject withdrawal criteria, medications permitted before and during the trial;
  - Methods for timing and assessing variables, procedures for monitoring subject compliance, specification of efficacy and/or safety parameters;
  - The methods and timing for assessing, recording, and analysing efficacy and/or safety parameters.

Impact on Data Collection

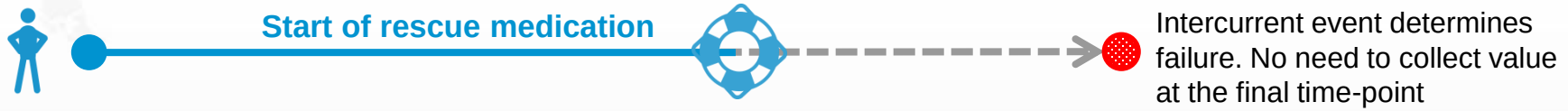
- The estimators chosen for the agreed **estimand dictate the data that need to be collected** during the trial.
- **Different estimands** (even within those targeted in one trial) might have **different requirements** regarding data collection.
- A trial design that is suitable for one estimand **might not be suitable** for other estimands of potential importance.

The **amount of patient withdrawals** from the study does **not influence** the relevance of a particular strategy or estimand, but the **impact** of potential patient withdrawals on estimation needs careful consideration.

Impact on Data Collection

- An estimand based on a **treatment policy strategy** requires the value for the variable to be **collected for all subjects regardless** (i.e. before and after) **of the intercurrent event**.

- In contrast, an estimand in which the variable is defined as a composite of no use of rescue medication and a favourable clinical outcome **does not require collection of data after the use of rescue medication**.



Efforts should be made to **collect all data that are relevant to support a statistical analysis aligned to the estimands of interest**, including data for the **characterisation, occurrence and timing of intercurrent events.**

Impact on data collection

- Missing data is inevitable in certain scenarios (e.g. administrative censoring, loss to follow-up); these potential scenarios should be well justified.
- However, in situations of treatment discontinuation, use of rescue medication, etc. **data can still be collected**. These data may not be relevant anymore, depending on the chosen strategy and estimator.
- For terminal events (e.g. death), data cannot be collected, but this is also **not missing data**.
- Data that are necessary to estimate the estimand but not collected will lead to a **missing data problem** that has to be **addressed through statistical inference** (with consequent issues regarding untestable assumptions and robustness of results).

Impact on data collection

- A **prospective plan to collect reasons** why data intended for collection are missing is helpful for distinguishing between intercurrent events and missing data.
  - Modify eCRFs to prompt collection of the reason for study withdrawal with **more granularity**, e.g. discontinuation due to patient's decision is not detailed enough.
  - A statement like "loss to follow-up" does not directly inform on treatment discontinuation, which should be **recorded separately**.
  - There should also be an indication if treatment discontinuation happened **due to lack of efficacy or toxicity**.

- Some measures can be implemented in the trial to reduce or avoid intercurrent events that would normally occur in clinical practice. It is important to ensure that they do not affect the **external validity** of the trial.

Design Options

- **Randomisation** and **blinding** remain cornerstones of controlled clinical trials. Several **non-standard designs** are available that can be aligned to the choice of the estimand or estimands that reflect the primary trial objectives:
  - **Enrichment designs:** incorporate a run-in period in which a subset of the subjects are selected based on their likelihood of experiencing the intercurrent event of interest, e.g., the population of interest could be patients who tolerate the experimental treatment.
  - **Randomised withdrawal designs:** all subjects are initially treated with the experimental treatment, then, subjects that have a positive response to the experimental treatment are randomly selected either to remain on the experimental treatment or to be switched to placebo or alternative control.
  - **Titration designs:** permit flexible dosing to accommodate individual differences in drug response which may allow more subjects to continue on the assigned treatment by reducing number of intercurrent events.

Not all types of design may be acceptable in all situations. Appropriate **dialogue** with regulators may be necessary.

Other important aspects

- A **precise description of the estimand(s)** of interest should inform **sample size calculations**.
- For **synthesising evidence across clinical trials**, the same estimand should be considered at the planning stage of the contributing trials.
  - Similar considerations apply, for example, to the design of a **meta-analysis, using estimated effect sizes from completed trials to determine non-inferiority margins,** or the use of external control groups for the **interpretation of single-arm trials**.
- A trial may have **multiple objectives translated into multiple estimands**.
  - Multiplicity adjustment for multiple endpoints or multiple sub-groups can equally be applied to multiple estimands.

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Next module:

2.5. Impact on trial analysis

Role and choice of sensitivity analysis and supplementary analysis in light of the estimand framework

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

Training Module 2.5: Impact on trial analysis

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- Module 3: Generic example

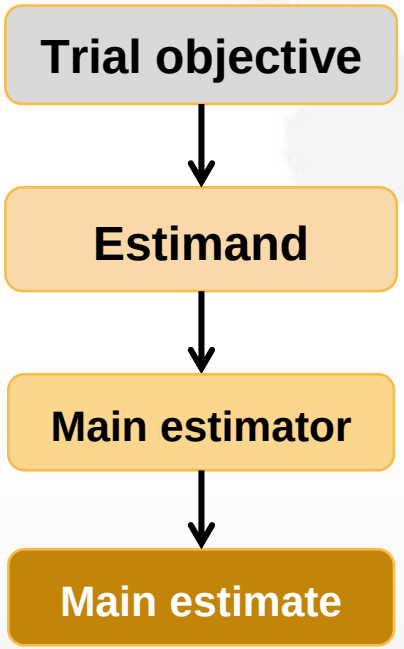
ICH E9(R1) – Table of Contents

Outline of Module 2.5

- Main estimation
- Sensitivity analysis
- Role of sensitivity analysis
- Choice of sensitivity analysis
- Supplementary analysis

Main estimation

- An analytic approach, or **estimator**, that is **aligned with a given estimand** should be implemented .
- For example, if addressing use of rescue medication with a **treatment-policy strategy**;
  - ✓ Analysis based on **continued data collection after the intercurrent event** and use of those observed data in the analysis would be **'aligned'** to the estimand, 👍
  - ✘ Not attempting to collect those data and/or regarding data after rescue medication as 'missing' then **analysing through MMRM with a MAR assumption** would **not be aligned** to the estimand. 👎



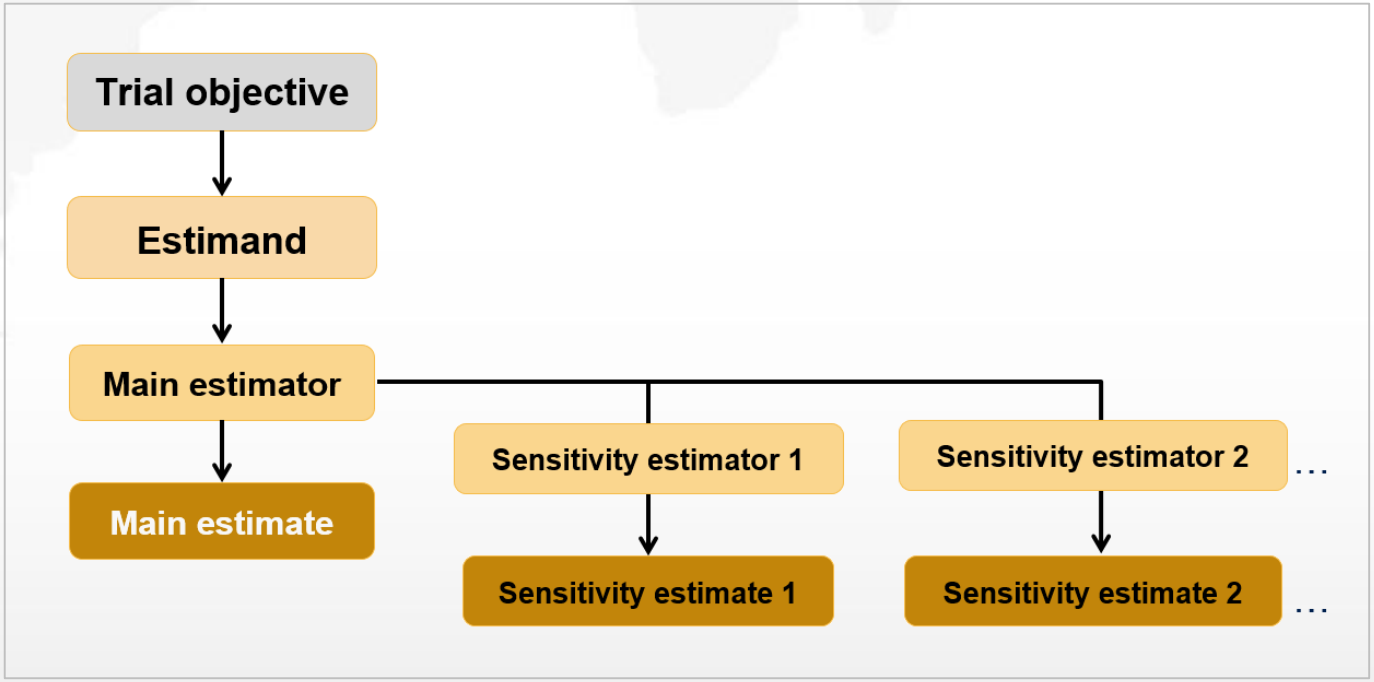
MMRM: Mixed Models for Repeated Measures
MAR: Missing At Random

Main estimation

- The **estimator** selected should be able to provide an **estimate** on which a **reliable interpretation can be based**.
- An important consideration for whether a reliable estimate will be available is the **number and plausibility of assumptions that need to be made** in the main analysis, including those associated with the use of modelling, prediction or imputation to address missing data.

Main estimation

- Any **assumptions made should be explicitly stated**, and **sensitivity analysis** should be used to assess the robustness of the results to the underlying assumptions, aligned to one estimand.



Sensitivity analysis

Sensitivity analysis Is 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) addendum

Main estimation: missing data

- The addendum calls for **greater precision on what is labelled as 'missing data'**.
- Assessments scheduled **after an intercurrent event has occurred** (e.g. discontinuation of treatment) **should not** automatically **be set to missing**. If the treatment policy strategy is selected, in particular, maximising the collection of post-intercurrent event data would limit the reliance on the assumptions on mechanisms for missingness.
- Having clarity in the estimand gives a basis for **planning which data need to be collected** and hence which data, when not collected, present a **missing data problem** to be addressed.

Missing data

Missing data Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.

Missing data definition, ICH E9(R1) addendum

Check slides 28 and 34 of Module 2.3

Main estimation: missing data

- For example:
  - If planning to address the use of rescue medication with the **treatment-policy strategy**, assessments scheduled after the use of rescue medication should continue as planned. Any assessments not taken are '**missing data**'.
  - If planning to address the use of rescue medication with **a hypothetical strategy**, the relevance of the assessments scheduled after the use of rescue medication for estimation depends on the estimator(s) chosen.
- **Methods to address** the problem presented by **missing data** can be selected to **align with the chosen estimand**.

Role of sensitivity analysis

- Sensitivity analysis is used to evaluate the **robustness of inferences** made on a particular estimand to **limitations in the data** and **deviations from the assumptions** used in the statistical model for the main estimator.
- With an agreed estimand, and a pre-specified statistical analysis that is aligned to that estimand, sensitivity analysis can focus on sensitivity to deviations from assumptions in respect of a particular analysis rather than sensitivity to the choice of analytic approach.

Role of sensitivity analysis

- In general, the **statistical assumptions** that underpin the main estimator should be **clearly documented**.
- **A sensitivity analysis**, focused on the same estimand, should then be **pre-specified** to investigate the impact of deviations from these assumptions. This might be characterised as the extent of departures from assumptions that change the interpretation of the results in terms of their statistical or clinical significance (e.g., tipping point analysis).
- Whilst the While on Treatment and the Composite strategies do not make estimating assumptions (but have to be justified in terms of **interpretability**), and in the Treatment Policy strategy the impact of assumptions can be reduced by maximising **data collection**, the Hypothetical and Principal Stratum strategies necessarily imply strong **assumptions**.

Supplementary analysis

- Supplementary analysis should be clearly **distinguished from sensitivity analysis**, and in general, should be given a **lower priority** relative to a sensitivity analysis.
- **Any other analysis** that is planned, presented or requested in order to more fully investigate and understand the trial data and the effects of treatment is referred to as a **supplementary analysis**.

Supplementary analysis

Supplementary analysis Is a general description for analyses that are conducted in addition to the main and sensitivity analysis to provide additional insights into the understanding of the treatment effect. The term describes a broader class of analyses than sensitivity analyses.

Supplementary analysis definition, ICH E9(R1) addendum

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Next module:

2.6. Documenting estimands and sensitivity analysis

Impact of the addendum on protocol writing, study design, data analysis and interpretation

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

Training Module 2.6 - Documenting estimands and sensitivity analysis

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- Module 3: Generic example

ICH E9(R1) – Table of Contents

Outline of Module 2.6

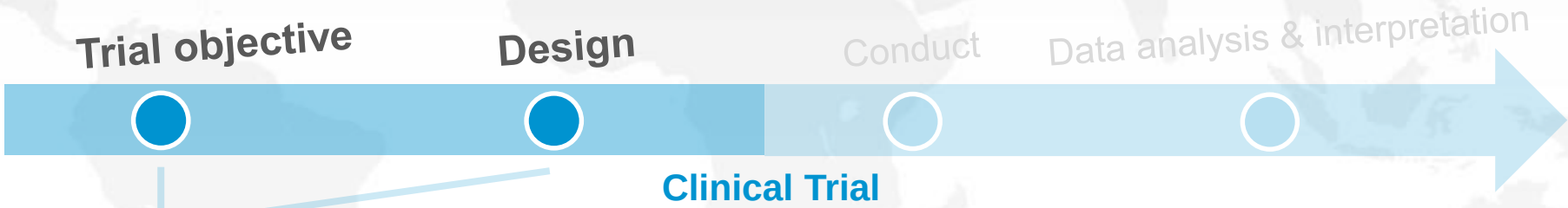
- Incorporating estimands and methods of estimation including suitable sensitivity analysis in the writing of a trial protocol and statistical analysis plan
- Reporting results in the Clinical Study Report
- Handling changes to an estimand

Incorporating estimands in protocol writing

Trial Protocol

- **Estimands** should be defined and explicitly specified in the clinical trial **protocol**.
  - Following identification of **intercurrent events**
- The primary estimand pre-specified in the trial protocol should correspond to the **primary trial objective**.
- The **protocol** and the **statistical analysis plan** should pre-specify the **main estimator** that is **aligned with the primary estimand** and leads to the **primary analysis.** Suitable **sensitivity analysis** should be planned to explore the robustness under deviations from its assumptions.

Incorporating estimands in protocol writing



Trial Protocol

- Estimands for **secondary trial objectives** (e.g., related to **secondary variables**) that are likely to support regulatory decisions should be defined and explicitly specified, each with a corresponding **main estimator.** Suitable **sensitivity analysis** should be planned.
- **Additional trial objectives** may be considered for exploratory purposes, leading to **additional estimands**.

Incorporating estimands in protocol writing

Trial Protocol

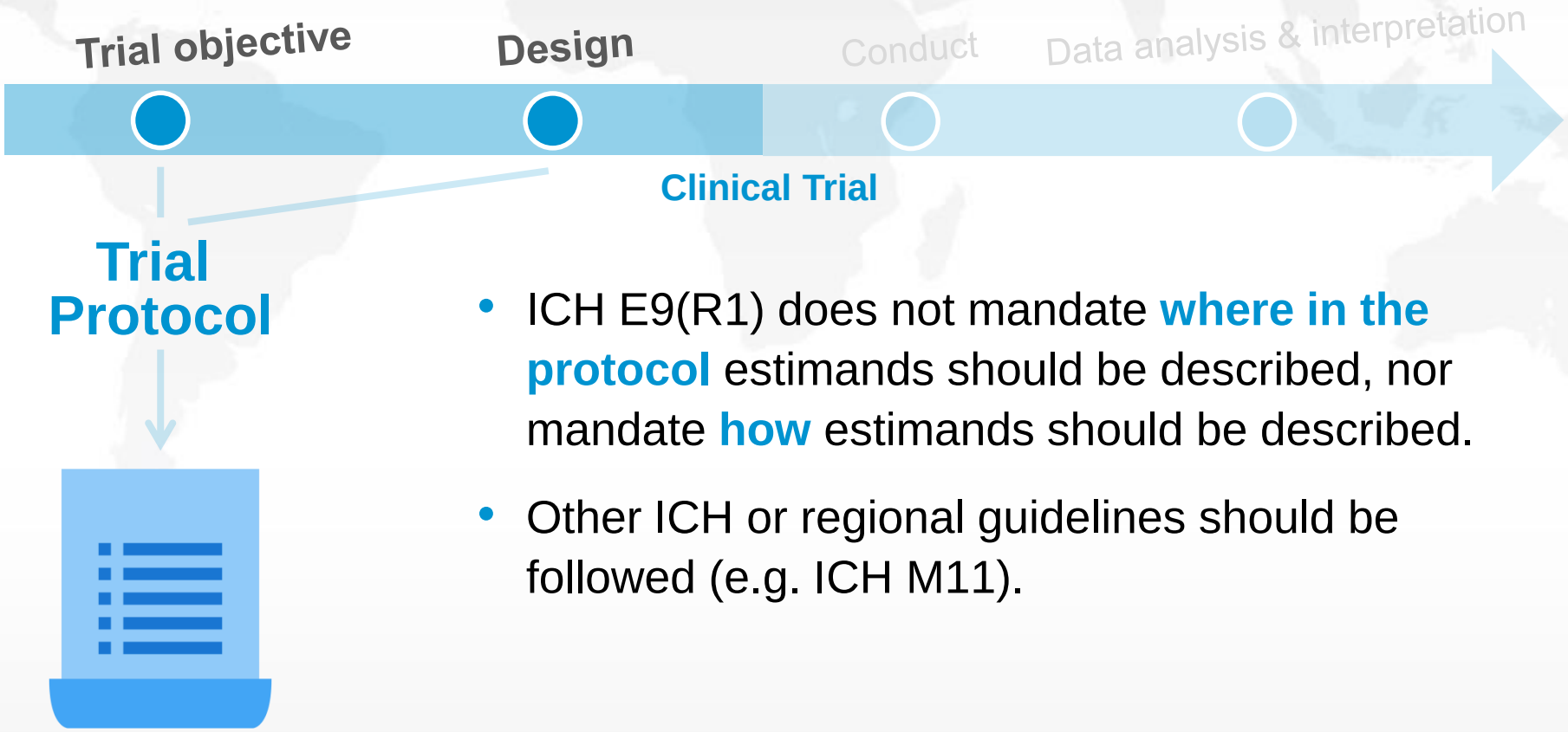
- When **secondary estimands** are of key interest, the trial should also be designed to account for them, and they should be **fully documented** in the protocol.
- It is preferable, although not a regulatory requirement, to also document an estimand for exploratory questions.

The **choice of the primary estimand** will usually be the main determinant for aspects of **trial design**.

Incorporating estimands in protocol writing

- The **trial analysis summarised in the protocol should be aligned with the primary estimand** with regards to (including but not limited to):
  - **Handling of intercurrent events**, for example:
    - Use of rescue medication;
    - Changes in permitted medications;
    - Switching treatments;
    - Discontinuing treatment;
    - Subject deaths.
  - The **selection of the data** to be included in the analyses.
  - **Details of the estimator**, including handling of missing data.
- Beyond these aspects, the conventional considerations for trial design, conduct and analysis remain the same.

Incorporating estimands in protocol writing



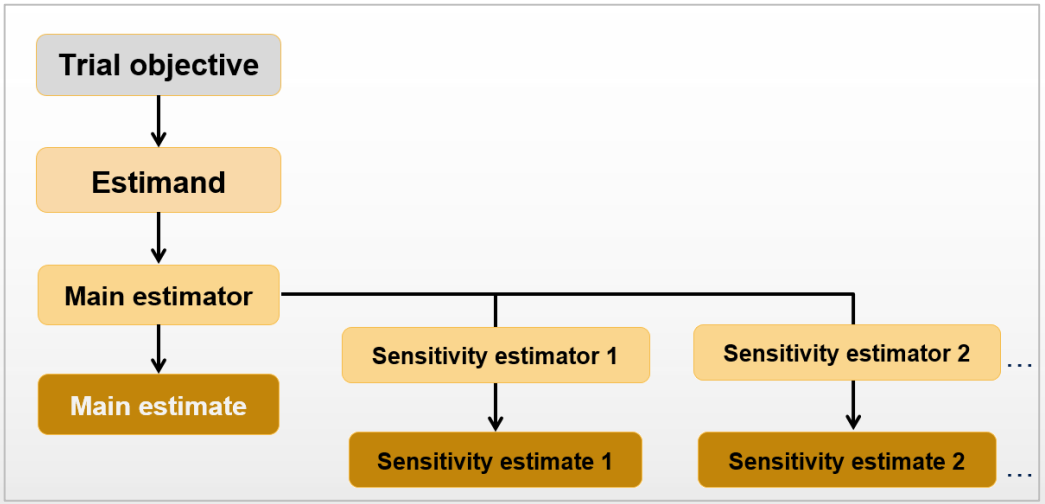
- ICH E9(R1) does not mandate **where in the protocol** estimands should be described, nor mandate **how** estimands should be described.
- Other ICH or regional guidelines should be followed (e.g. ICH M11).

Incorporating estimands in the SAP

Trial Protocol

Statistical Analysis Plan

- Full details of the planned statistical analyses should align with the estimand(s) defined, and not the other way around!



SAP: Statistical Analysis Plan

Potential impact on study conduct

- All efforts should be made to **define** the primary estimand **before the beginning of the trial**, as changes to it would be problematic and reduce its credibility.
- The occurrence of anticipated intercurrent events should be **monitored during the study**.
- The impact of any **unanticipated intercurrent events** occurring and/or other study conduct issues possibly affecting the primary estimand should be evaluated.
- A change in the primary estimand would usually require a **protocol amendment**.

Data analysis and interpretation

- Results from the main, sensitivity and any supplementary analyses should be **reported systematically** in the clinical trial report, specifying whether each analysis was **pre-specified, introduced while the trial was still blinded, or performed post hoc**.
- Summaries of the **number and timings of each intercurrent event** in each treatment group should be reported.

Data analysis and interpretation

- For **intercurrent events that were not foreseen** at the design stage, and were identified during the conduct of the trial with no possibility to formally amend the estimand specified in the protocol, the sponsor should:
  - explain how the unforeseen intercurrent events were **handled for estimating treatment effects in the analysis**;
  - explain the impact on what the revised analysis estimates for the treatment effect (i.e. the **impact on the pre-specified estimand**).

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Next module:

3. Generic example

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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

International Council for Harmonisation of Technical Requirements
for Registration of Pharmaceuticals for Human Use

Disclaimer

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

The presentation does not represent official guidance or policy of authorities or industry and it does not provide additional guidance beyond ICH E9(R1).

Legal Notice

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**

ICH E9(R1) – Table of Contents

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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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Check Module 2.1

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)**.

Check 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.

SBP: Systolic blood pressure

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
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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).

SBP: Systolic blood pressure

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
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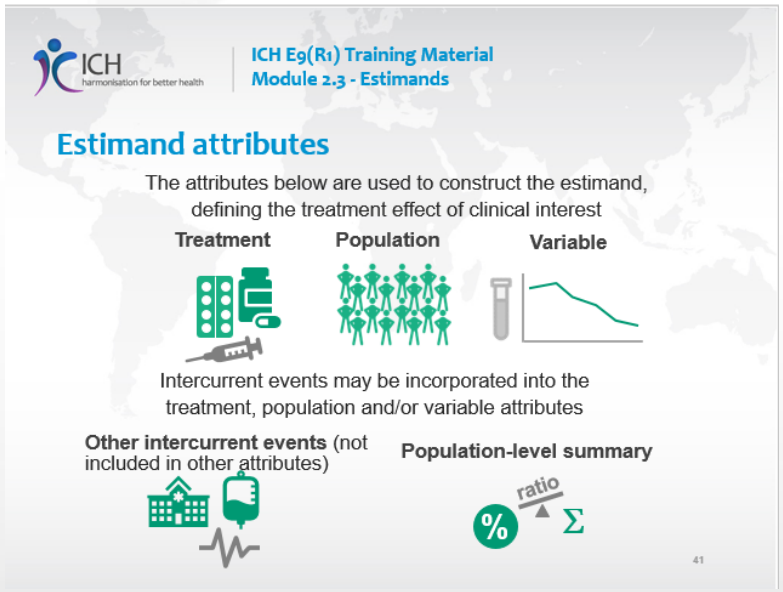
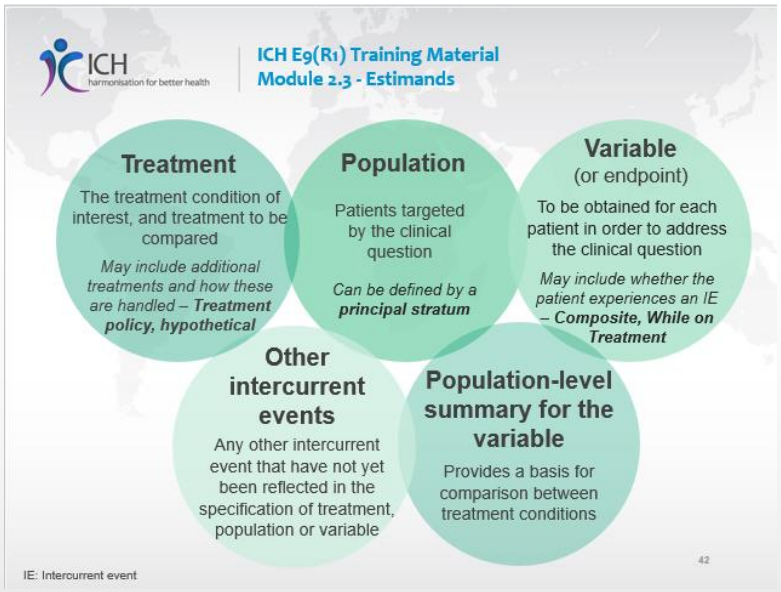
Check Module 2.3

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).





Check Module 2.3

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).

SBP: Systolic blood pressure

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).

SBP: Systolic blood pressure

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).

SBP: Systolic blood pressure

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)**
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

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)**.

* This is not an indication of regulatory preference or policy
SBP: Systolic blood pressure

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.

SBP: Systolic blood pressure

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.

* This is not an indication of regulatory preference or policy
SBP: Systolic blood pressure

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)**.

* This is not an indication of regulatory preference or policy
SBP: Systolic blood pressure

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.

SBP: Systolic blood pressure

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.

* This is not an indication of regulatory preference or policy
SBP: Systolic blood pressure

A thinking process…

1. Therapeutic setting and intent of treatment determining a trial objective
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3. Discuss strategies to address intercurrent events
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7. Document the chosen estimands

Check Module 2.4

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.**

Check Module 2.4

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.

SBP: Systolic blood pressure

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.

SBP: Systolic blood pressure

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

SBP: Systolic blood pressure
ANCOVA: Analysis of covariance

* This is not an indication of regulatory preference or policy

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
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6. **Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions**
7. Document the chosen estimands

Check Module 2.5

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.

SBP: Systolic blood pressure
ANCOVA: Analysis of covariance

* This is not an indication of regulatory preference or policy

Check Module 2.5

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.

ANCOVA: Analysis of covariance

A thinking process…

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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**

Check Module 2.6

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.

Check Module 2.6

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.

Check Module 2.6

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.

Check Module 2.6

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