Draft (Step 2) guideline 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

June 2018

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

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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 and case studies 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
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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 scientific questions of interest by defining suitable **estimands**.
- An **estimand** defines the target of estimation for a particular trial objective (i.e. “what is to be estimated”).

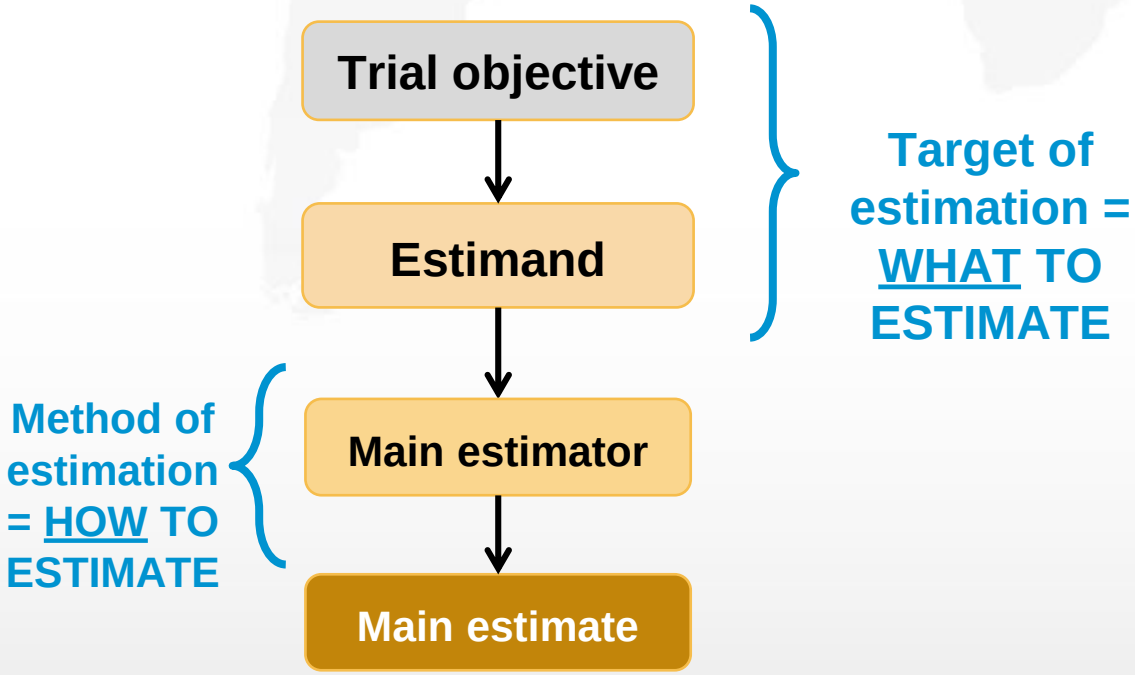
Summary

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.

Summary

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



Summary

- The addendum aims to facilitate dialogue regarding the treatment effects that a clinical trial should seek to estimate:
  - **between disciplines** (medics, statisticians, etc).
  - **between sponsor and regulator**.

- 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.

Check Module 2.3

Summary

- The description of an estimand will not be complete without reflecting how potential **intercurrent events** are addressed in the scientific question of interest.
- **Intercurrent events** have the potential to occur after treatment initiation and either preclude observation of the variable or affect its interpretation, e.g.:
  - use of an alternative treatment, perhaps a rescue medication;
  - discontinuation of treatment;
  - terminal events such as death.
- Study discontinuation, loss-to-follow-up or other missing data are **not intercurrent events** and are not reflected in the estimand, but instead represent limitations to the data to be addressed in the analysis.

Check Module 2.3

Summary

- Different **strategies** are available for how to address potential **intercurrent events** to reflect the scientific question of interest.
- The **choice of strategy** for each intercurrent event should be the subject of **multi-disciplinary discussion** between, e.g. statisticians and clinicians, and discussion between sponsor and regulator.
- The disease setting and the aim of treatment will influence the choice of strategy.
- Different strategies can be used alone or in combination to address multiple different intercurrent events.

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 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.

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.

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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.

Draft (Step 2) guideline ICH E9(R1)

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Training module 2.1: Introduction

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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 risk-benefit**.
  - In addition to evidence that is statistically compelling evidence of efficacy, assessment of efficacy considers the **magnitude of the beneficial 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 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 require additional medication, others will not…

Different treatment effects can be constructed.

Check draft 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 **strata of this population** that can **adhere to treatment**.

Check draft 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 **strata of this population** that do not require additional medication.

Check draft addendum section A.3.2!

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 either preclude observation of the variable or affect its interpretation.
- 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.

- Before designing and analysing a clinical trial it should be clear **which treatment effects are of interest**:
  - for **regulatory decision making**;
  - for optimal **communication of treatment effects** to patients, prescribers and other stakeholders.

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

- 'Treatment policy' is based on assessments **regardless of what happens to patients** (discontinuation of treatment, use of additional medications etc.).
- Data from those assessments are used in the statistical analysis for measuring treatment effects.

Is that what we want to know for decision making?

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

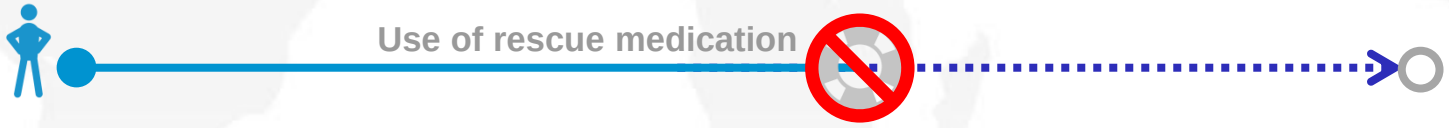
Example: Type II diabetes mellitus

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

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 on reaching agreement over what to estimate: **the estimand.**

Estimand

Estimand Is the target of estimation to address the scientific question of interest posed by the trial objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

Estimand definition, ICH E9(R1) Draft 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 that occur after treatment initiation and either preclude observation of the variable or affect its interpretation.

Intercurrent events definition, ICH E9(R1) Draft 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!

Check draft 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 (at least) **five strategies** that can be used alone or in combination to **address multiple different intercurrent events.**
  - Treatment policy
  - Composite
  - Hypothetical
  - Principal stratum
  - While on treatment

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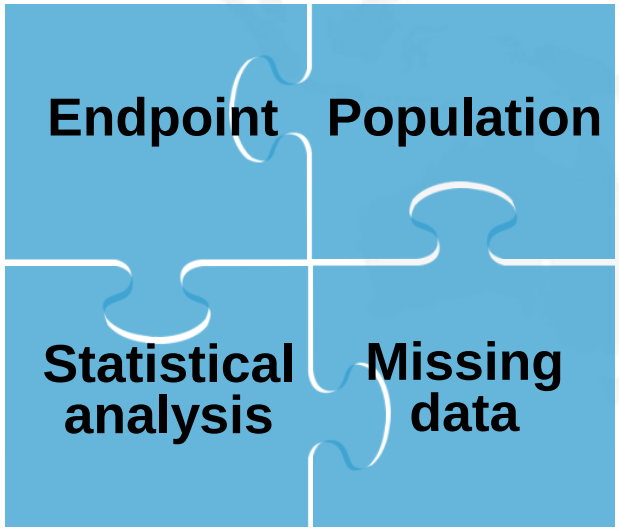
Concerns with current practice

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 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

- Targets of estimation, once identified, might **not be relevant to decision makers** (e.g. regulators, HTA bodies, payers, prescribers and patients):
  - Different treatment effects might be relevant to different decision makers.

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 are more likely to 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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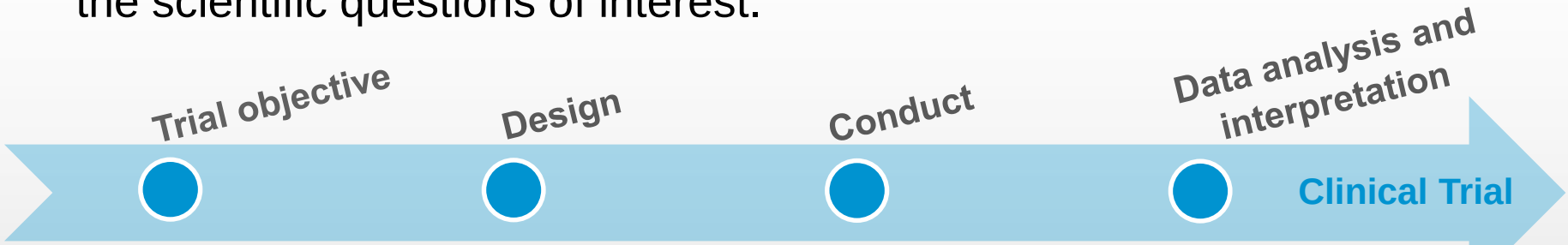
Scope of the addendum to ICH E9

Framework

A framework and language are introduced to:

- Promote **alignment between trial objectives, design (data collection), 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;
- 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:**
  - i.e. 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:
  - in **other phases of clinical development**, including post-authorisation;
  - in **clinical trials** and in **observational studies**;
  - 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: case studies

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:**
  - Patient are followed to observe MACE events, often over a period of years.

MACE: Major adverse cardiac events

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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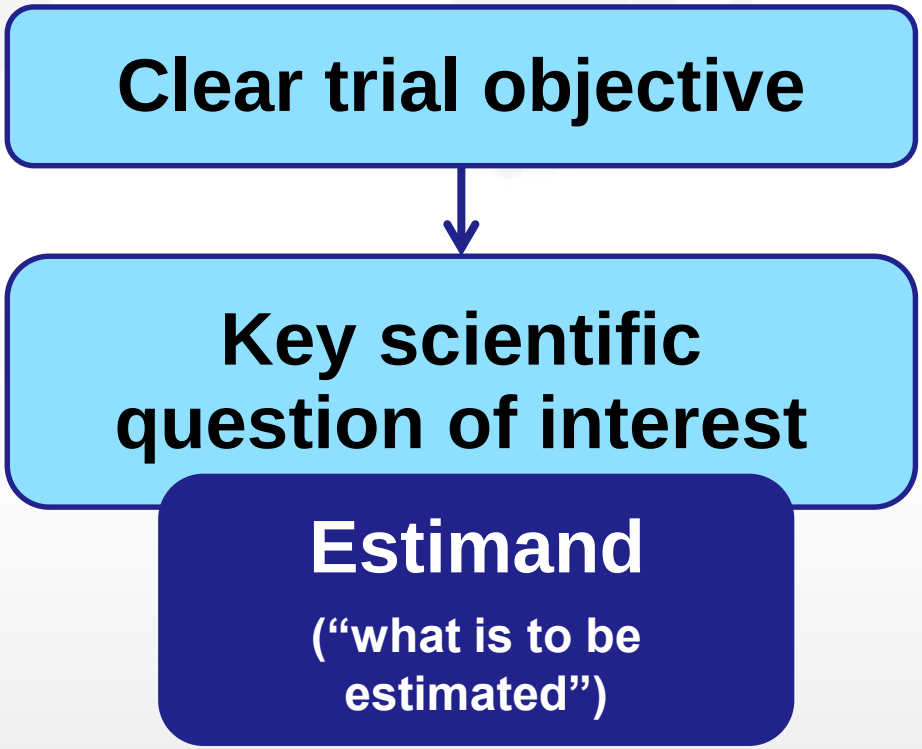
Outline of Module 2.2

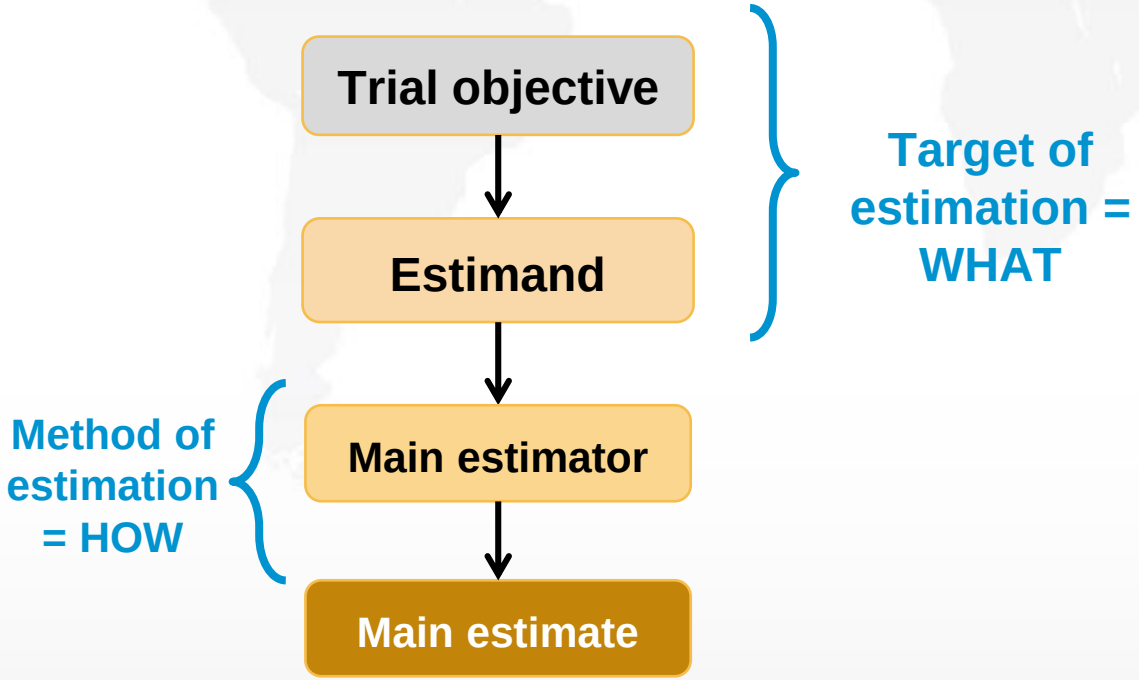
- A new framework for clinical trials
- Alignment between trial objective, design, planning, conduct, analysis and interpretation
- How this framework can improve discussions between sponsors and regulators on the suitability of designs and the interpretation of results

A 'new' framework

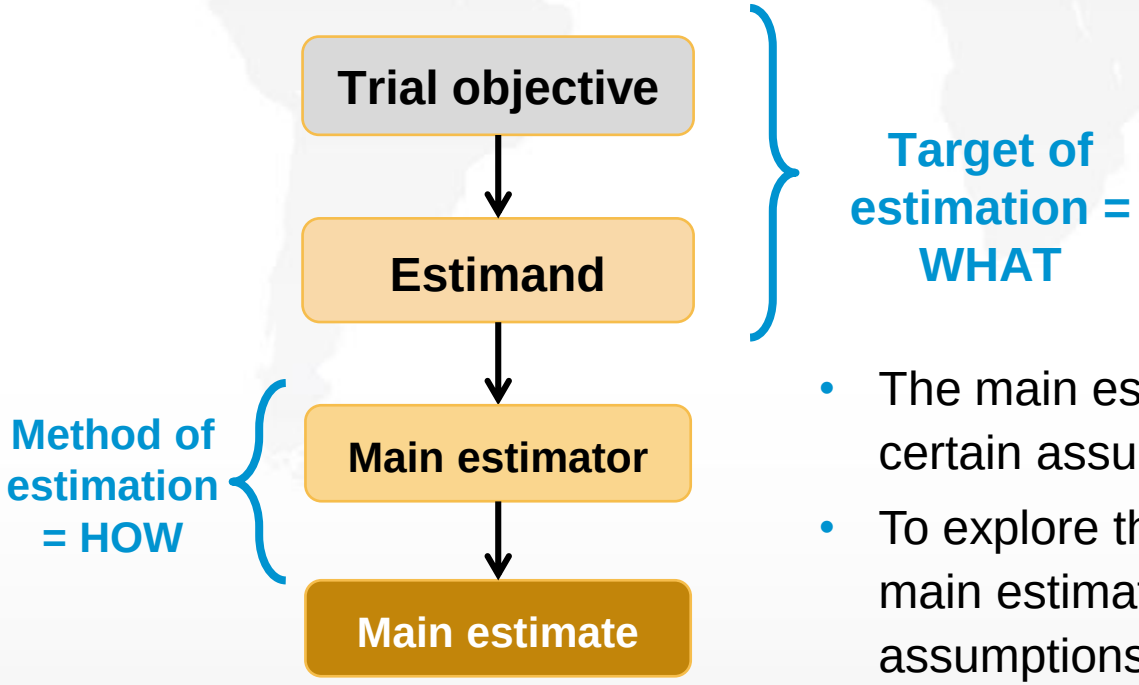
Clear trial objectives should be translated into key scientific questions of interest by defining suitable estimands.



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

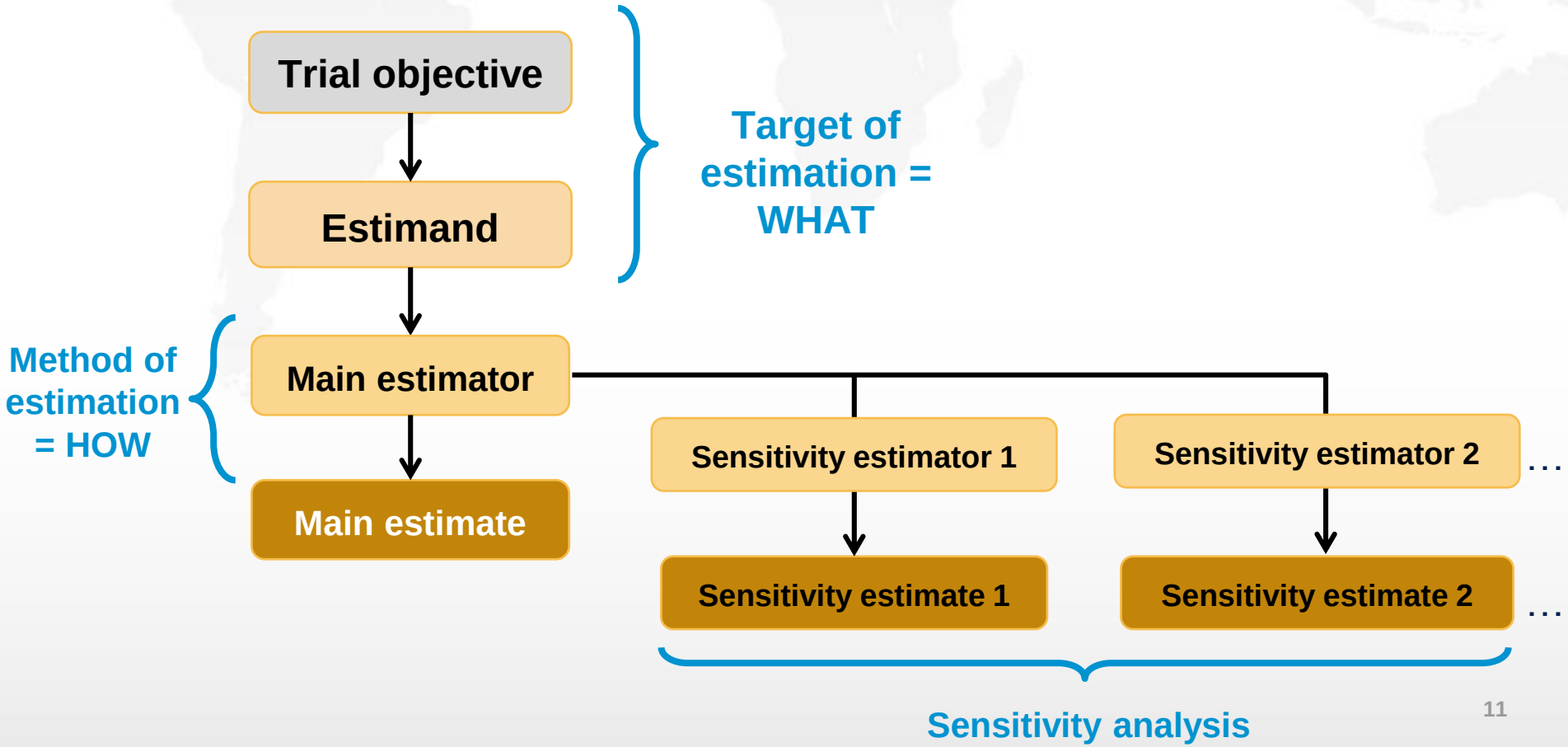


Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective



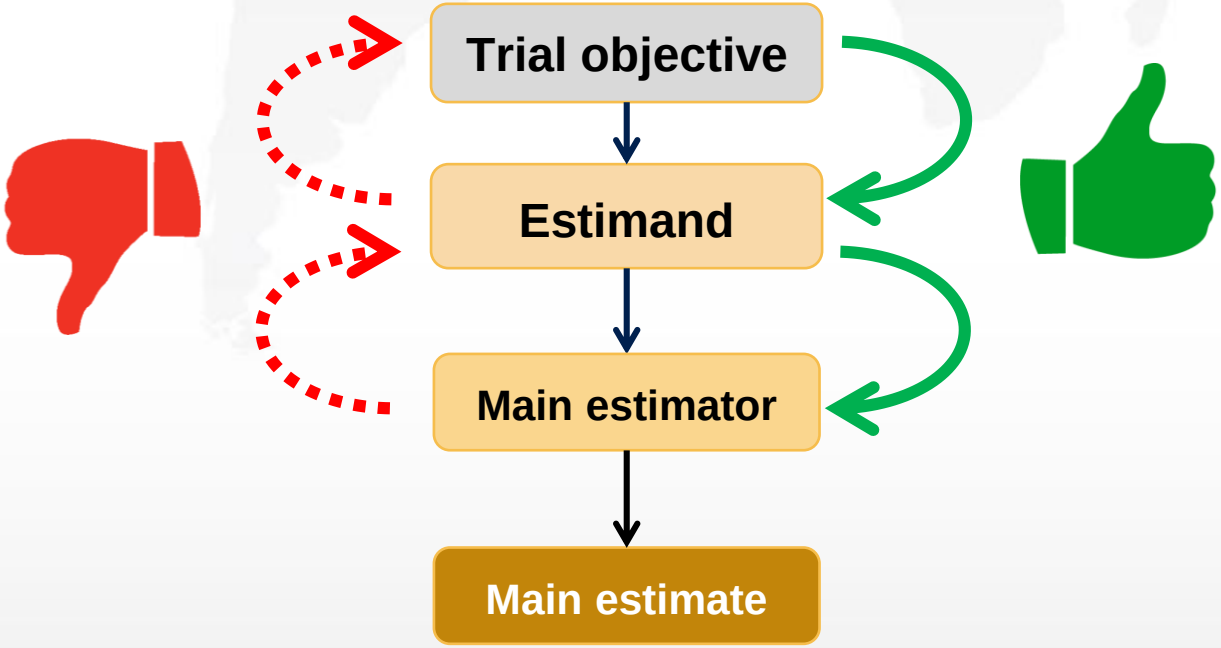
- The main estimator will be underpinned by certain assumptions.
- To explore the robustness of inferences from the main estimator to deviations from its underlying assumptions, sensitivity analysis should be conducted, in form of one or more analyses, targeting the same estimand.

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

In general, it is **important to proceed sequentially**. The trial objective should determine the choice of estimands and the estimands should determine the choice of estimators, not the reverse.



Where significant issues exist to derive a reliable estimate for a particular estimand, the trial objectives need to be re-considered from top-down to main estimator (**green** arrows). The main estimator should never define the trial objective from bottom-up (**red** arrows).

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

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Draft (Step 2) guideline 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
June 2018

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).

The current slide deck reflects the content on the Draft ICH E9(R1) addendum up to the time of its publication for public consultation. Content may be changed as a result of the consultation phase.

Legal Notice

Introduction note

These slides were produced as training material to accompany the Draft 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 and case studies 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

- Four attributes (A through D) that together describe an estimand
- Strategies for addressing intercurrent events
- General considerations for the construction of estimands
- Therapeutic and experimental considerations for the construction of estimands

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Module 2

A.3.1. Description

A.3.2 Strategies for addressing intercurrent events

A.3.3 Construction of estimands

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?

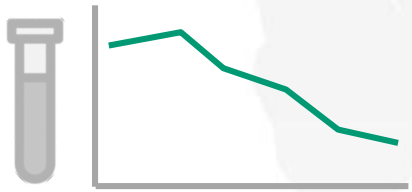
e.g. had they not received the treatment or had they received a different treatment.

- **Intercurrent events** need to be considered.
  - The occurrence of intercurrent events may depend on treatment conditions (e.g. had they not received the treatment or had they received a different treatment) which can impact data collected to assess clinical outcomes.
- **An estimand defines in detail what needs to be estimated to address a specific scientific question of interest.**
  - A description of an estimand includes **four attributes**.

Description of an estimand

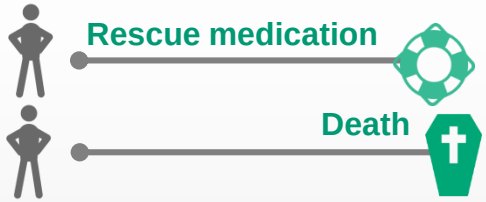
Population

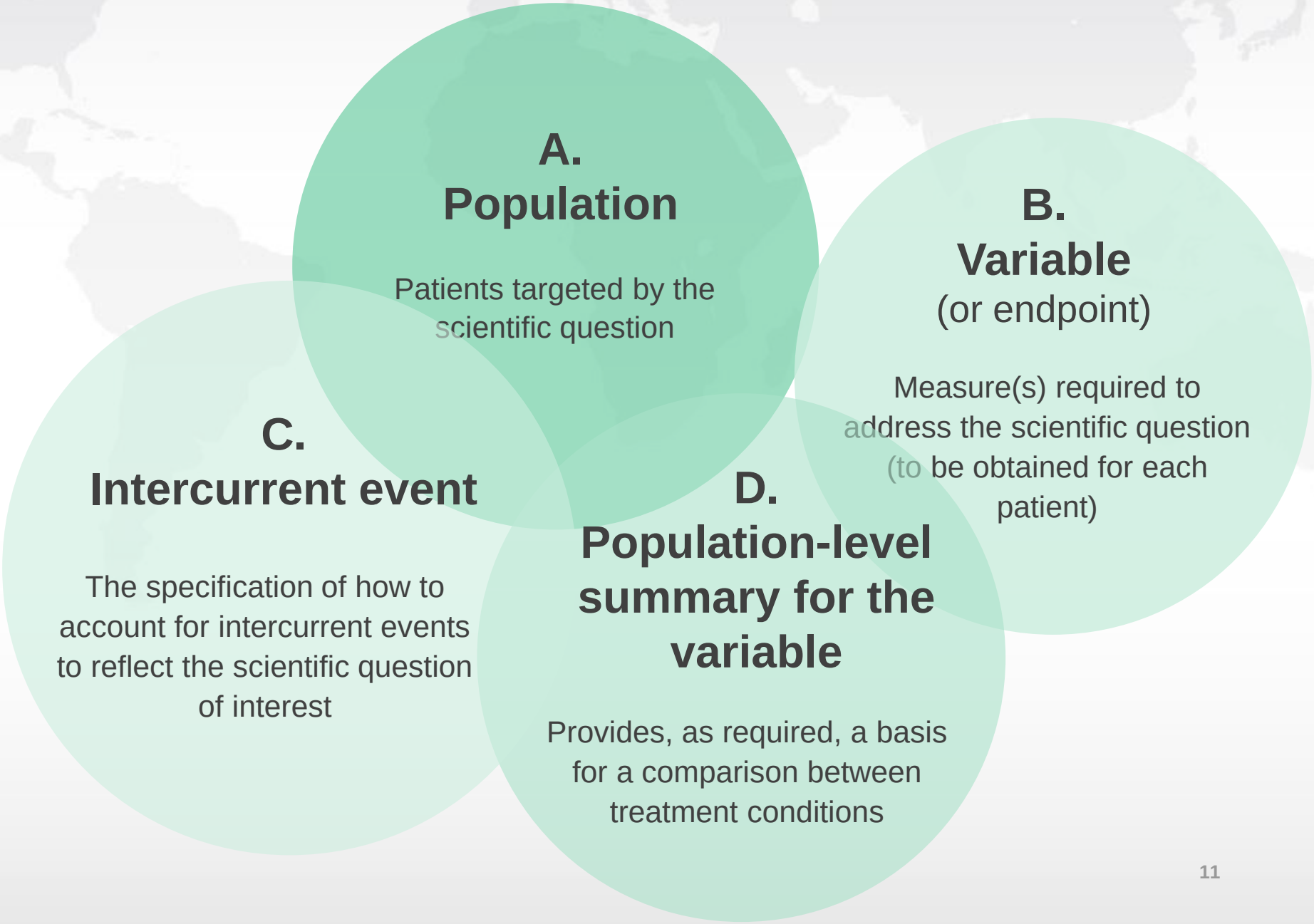
Variable



Population-level summary

The description of an estimand will not be complete without reflecting how potential **intercurrent events** are addressed in the scientific question of interest.




A.
Population
Patients targeted by the scientific question
B.
Variable
(or endpoint)
Measure(s) required to address the scientific question (to be obtained for each patient)
C.
Intercurrent event
The specification of how to account for intercurrent events to reflect the scientific question of interest
D.
Population-level summary for the variable
Provides, as required, a basis for a comparison between treatment conditions

A.
Population

B.
Variable
(or endpoint)

Measure(s) required to address the scientific question (to be obtained for each patient)

C.
Intercurrent event

The specification of how to account for intercurrent events to reflect the scientific question of interest

D.
Population-level summary for the variable

Provides, as required, a basis for a comparison between treatment conditions

Together these attributes describe the

estimand

defining the target of estimation.

Description of an estimand

A. Population

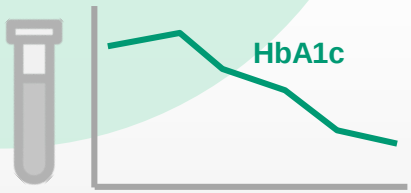
Patients targeted by the scientific question

- The population is typically characterised through **inclusion/exclusion criteria in the study protocol**.
- In some cases a subgroup is of interest
  - defined by a baseline characteristic;
  - defined in terms of a potential intercurrent event, for example, the **stratum** of patients who can tolerate and remain on treatment.
- Note the important difference in how the **subgroup** (baseline characteristics) and the **stratum** (potential intercurrent event once treatment is received) are defined.

Description of an estimand

B.
Variable
(or endpoint)

Measure(s) required to address the scientific question (to be obtained for each patient)



- The variable typically consists of
  - **measurements** taken: e.g. blood pressure;
  - **functions** thereof: e.g. change from baseline to one year in HbA1c;
  - quantities related to **observed events:** e.g. time of death, number of relapses.
- The variable may also be used to address **intercurrent events** such as discontinuation of intervention
  - using measurements taken prior to discontinuation of treatment (e.g., AUC of HbA1c until discontinuation);
  - or using composites (e.g., treatment failure defined as non-response or treatment discontinuation).

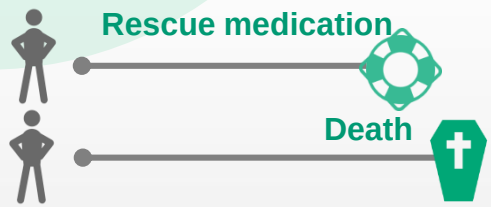
HbA1c: Glycated haemoglobin
AUC: Area under the curve

Check definition of IE in Module 2.1

Description of an estimand

C. Intercurrent event

The specification of how to account for intercurrent events to reflect the scientific question of interest

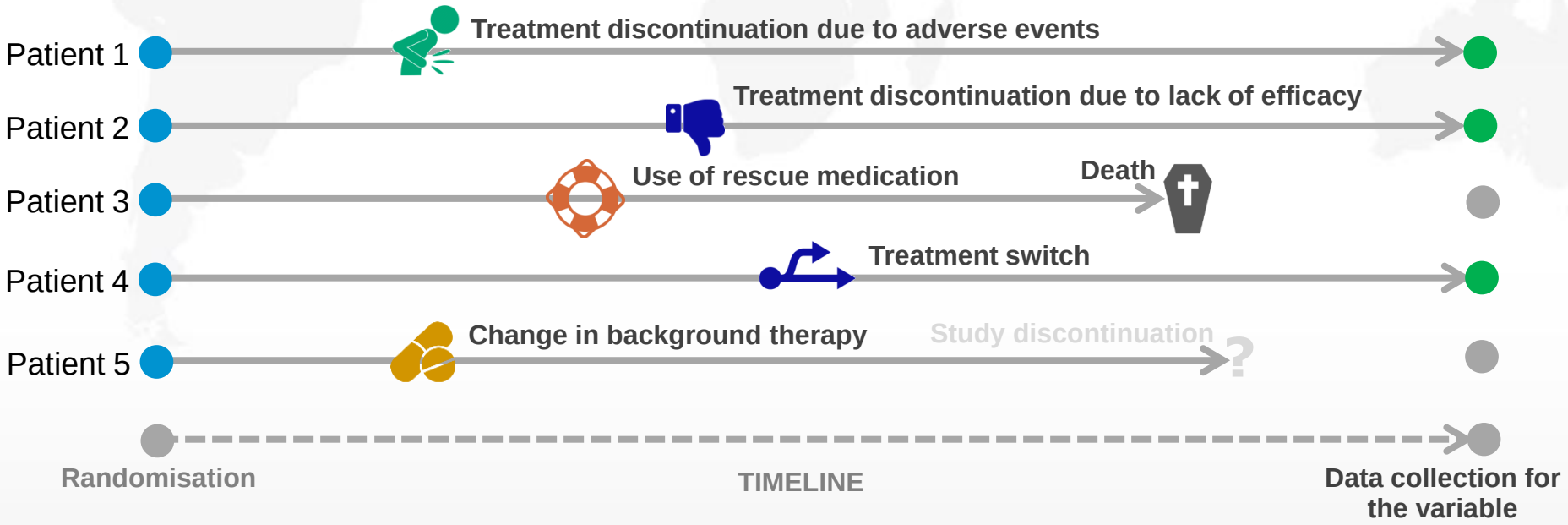


- Intercurrent events can present in **multiple forms** and can affect the interpretation of the variable.
- Clinical trials are typically faced with **more than one type of intercurrent event**.
- The set of intercurrent events for consideration will depend on the specific therapeutic setting and trial objective.

IE: Intercurrent event

Description of an estimand

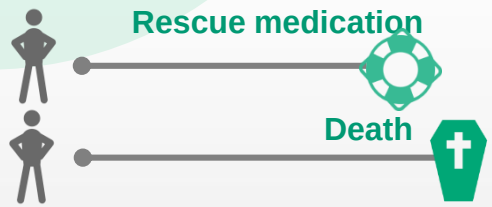
Intercurrent events



Description of an estimand

C. Intercurrent event

The specification of how to account for intercurrent events to reflect the scientific question of interest



- **How to account for intercurrent events?**
- For example, accounting for it…
  - …as part of the variable (composite strategy, while-on-treatment strategy);
  - …by disregarding its occurrence / as part of the treatment (treatment-policy strategy);
  - …as part of the population (principal stratification strategy) or;
  - …as model-based predictions under the originally randomised treatment (hypothetical strategy).

Missing data

- Intercurrent events are **not a missing data problem**. Loss-to-follow-up is not generally regarded as an intercurrent event. Indeed missing data and loss-to-follow-up are irrelevant to the construction of the estimand.

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) Draft addendum

Description of an estimand

D. Population-level summary for the variable

Provides, as required, a basis for a comparison between treatment conditions.

- 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

A.
Population

Patients targeted by the scientific question

B.
Variable
(or endpoint)

Measure(s) required to
entific question
(to be obtained for each
patient)

C.
Inter

The specification of how to account for intercurrent events to reflect the scientific question of interest

D.
Population-level summary for the variable

Provides, as required, a basis for a comparison between treatment conditions

The estimand attributes A through D are inter-related and should not be considered independently.

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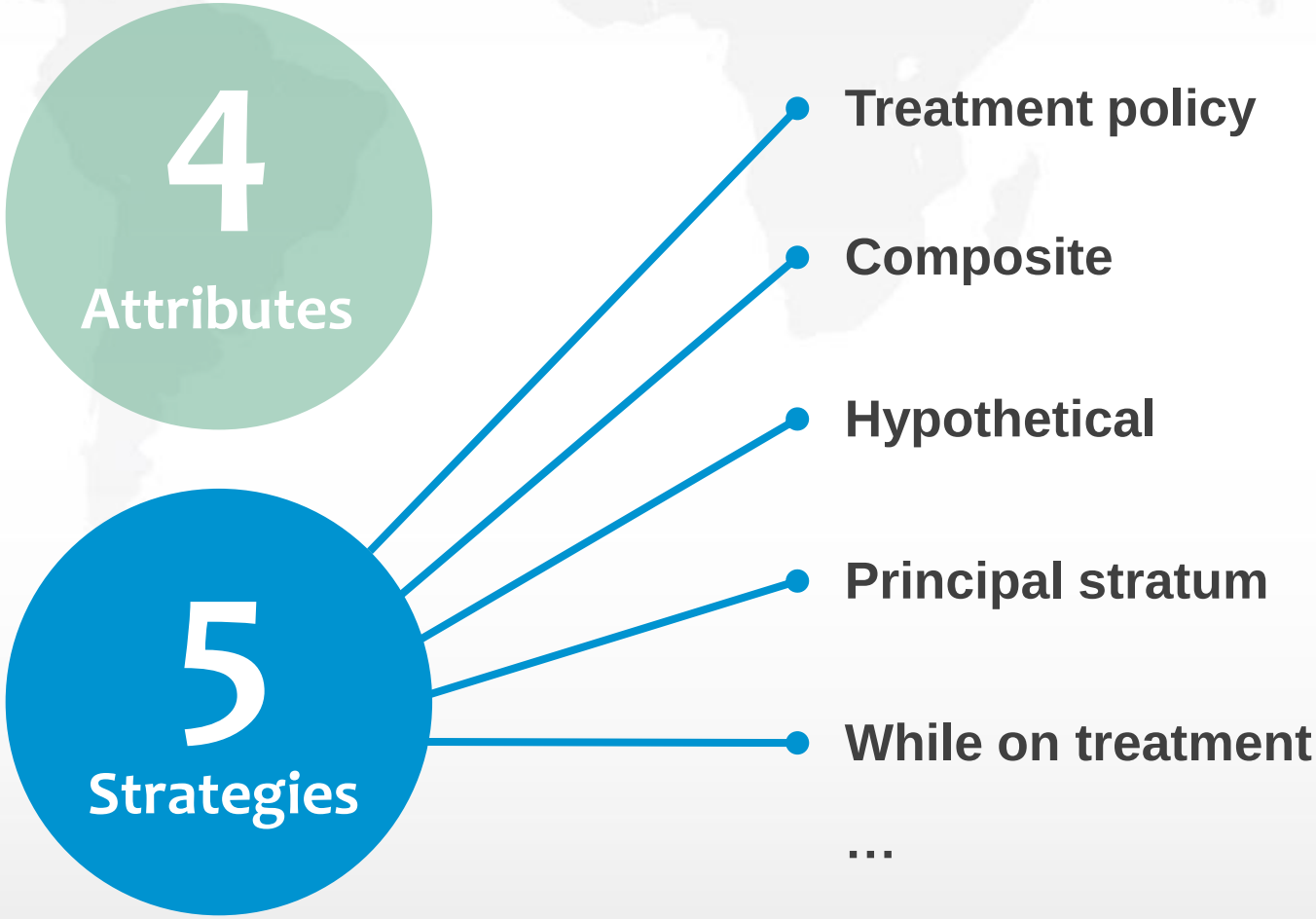
Module 2

A.3.1. Description

A.3.2 Strategies for addressing intercurrent events

A.3.3 Construction of estimands

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



Strategies for addressing intercurrent events

- … to consider when addressing **different intercurrent events**.
- A strategy is chosen for each intercurrent event to reflect the scientific question of interest; different strategies can be used for different intercurrent events.
- 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?

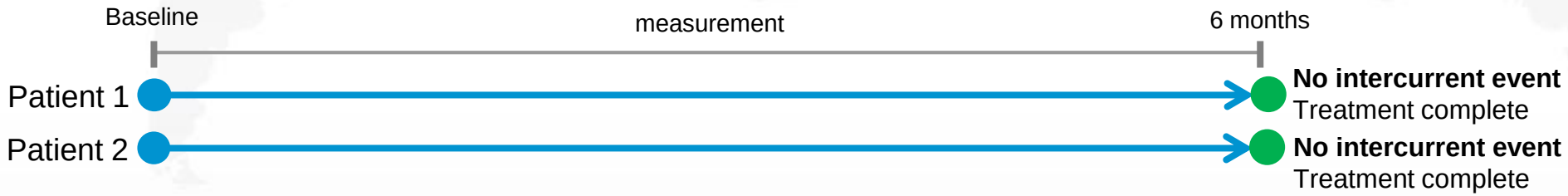
Let's take an example…

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

- **Response to treatment:** monitored monthly **(continuous measurement)**.
- **Main scientific question: comparison of Drug X to placebo at month 6 →** best addressed by a randomised clinical trial.
- **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 **3 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…

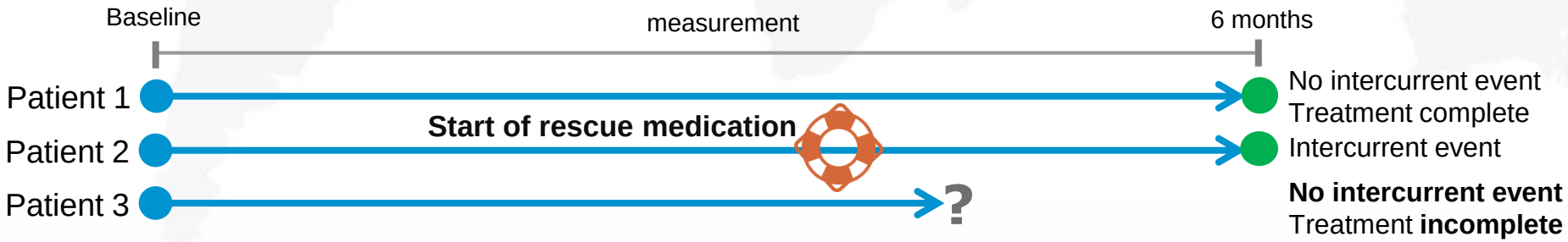
Strategy labels are just for ease of reference

1. Treatment-policy strategy

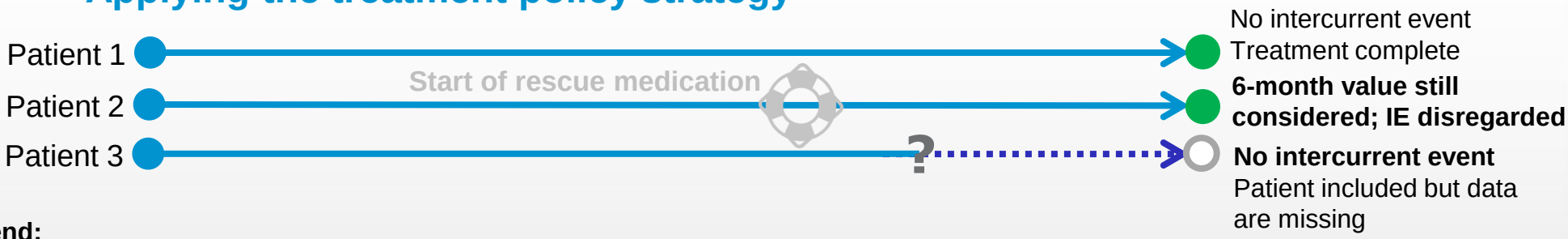
- In this strategy, the occurrence of the intercurrent event is **irrelevant**:
  - the data collected for the variable of interest are used **regardless of whether or not the intercurrent event occurs.**
- For example, when specifying how to account for rescue medication as an intercurrent event, occurrence of the intercurrent event is ignored (disregarded) and the observations collected after use of rescue medication for the variable of interest are used.
- In general, this strategy **cannot be implemented** when values for the variable after the intercurrent event **do not exist for all subjects**.
  - 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
- ? Patient lost to follow-up
- Intercurrent event (IE) - in grey when disregarded
- Part of patient time course considered
- Part of patient time course not observed and needs to be imputed/predicted

Strategy labels are just for ease of reference

2. Composite strategy

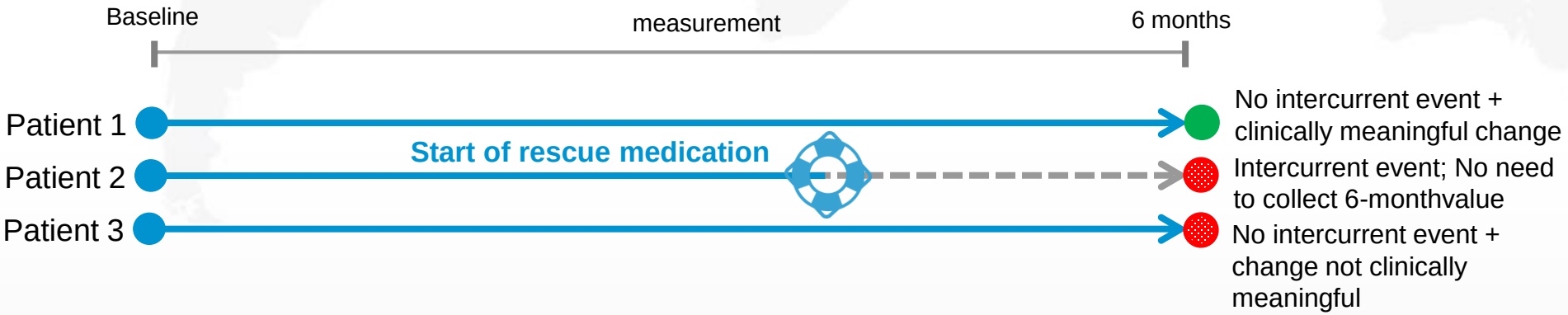
- In this strategy, the occurrence of the **intercurrent event** is taken to be **a component of the variable**, i.e. the intercurrent event is integrated with one or more other measures of clinical outcome as the variable of interest.
  - For example, the variable might be defined as a **composite of no use of rescue medication and a favourable clinical outcome**, i.e. patient becomes a non-responder if they need to use rescue medication.
  - Alternatively, for a **numerical variable**, experiencing an intercurrent event might be ascribed an **extreme unfavourable value** and a suitable summary measure selected (e.g. median or trimmed mean).

2. Composite strategy

- Sometimes an **event** being considered as intercurrent is itself the **most meaningful variable** that can be measured for quantifying the treatment effect of interest.
  - This can be the case with death: the fact that a subject has died may be much more meaningful than observations before death, and observations after death will not exist.

2. Composite strategy - 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 the composite strategy**



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

Legend:

- 6-month value has been collected and outcome is positive
- 6-month value has been collected and outcome is negative
- 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.

Strategy labels are just for ease of reference

3. Hypothetical strategy

- In this strategy, 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 to reflect that scientific question of interest is that 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 will need to be implicitly or explicitly **predicted / imputed**.

3. Hypothetical strategy

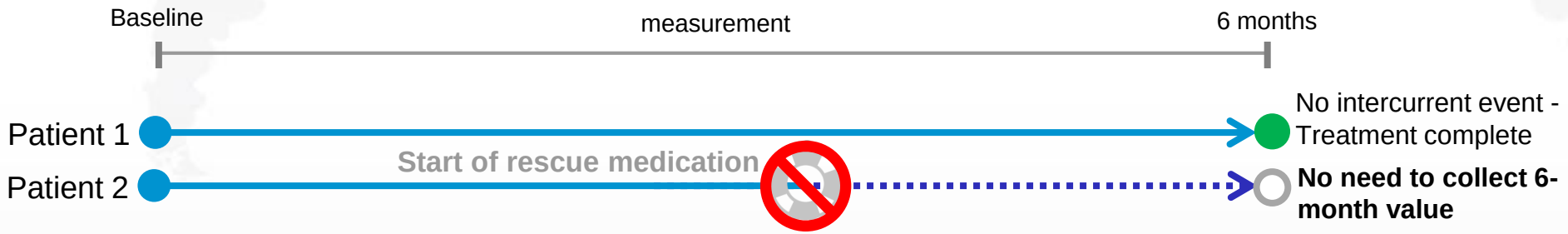
Important to keep in mind…

- The hypothetical scenario **should consider reasonable situations**, e.g. a scenario where a toxic medicine is considered to be non-toxic is not usually relevant for decision making.
- Care is required to **precisely describe** the hypothetical conditions reflecting the scientific question of interest in the context of the specific trial.

3. Hypothetical strategy - example

- The **estimand** assesses the treatment effect in an alternative, hypothetical setting where rescue medication was not available to subjects.

- **Applying the 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 and needs to be imputed/predicted
- Intercurrent event hypothetically not present. Time of intercurrent event marks the end of data collection.

Strategy labels are just for ease of reference

4. Principal stratum strategy

- In this strategy, principal stratification is defined by a **patient's potential intercurrent events on either or both treatments.**
  - It is a subset of the broader population;
  - For example, patients who can tolerate and remain on either treatment; the target population is then considered to be the stratum in which an intercurrent event would not occur in either group;
  - A specific stratum or several strata could be of interest, e.g. adherence to treatment regardless of adherence to control.
- The scientific question of interest relates to the treatment effect **only within that stratum / those strata**.
  - Effects in principal strata should be clearly distinguished from any type of subgroup or per-protocol analyses where membership is based on the trial data.

4. Principal stratum strategy

- 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.

4. Principal stratum strategy - example

- A given patient can receive either treatment or placebo.
- When receiving treatment some patients will use rescue medication, others not. The same applies for patients on placebo.
- The **estimand** assesses the treatment effect in the stratum of patients which would not use rescue medication regardless to which treatment arm they would be assigned.

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

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

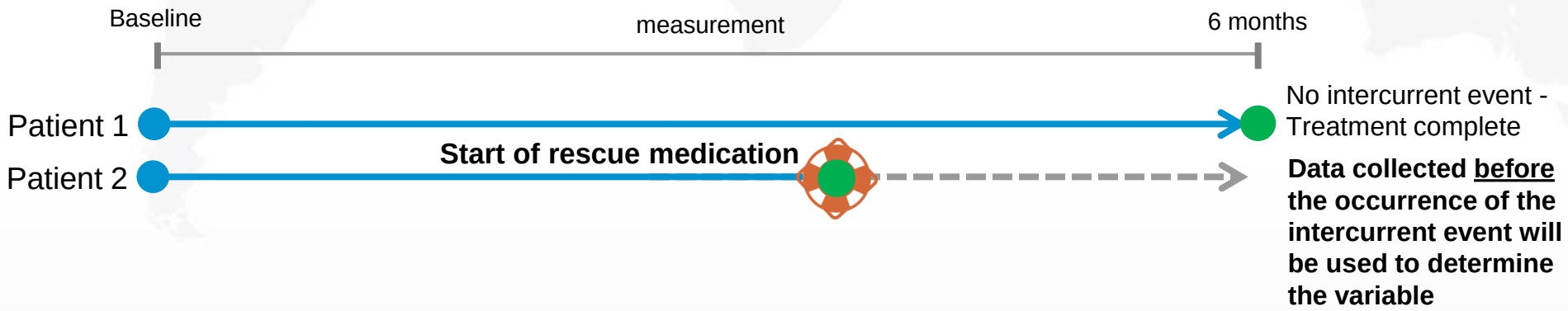
Strategy labels are just for ease of reference

5. While on treatment strategy

- In this strategy, 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 purely symptomatic treatment because they die, yet it is relevant to measure the success of the treatment based on the effect on symptoms before death.
    - 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.

5. While on treatment strategy - 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 the 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).

Multiple intercurrent events – example

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

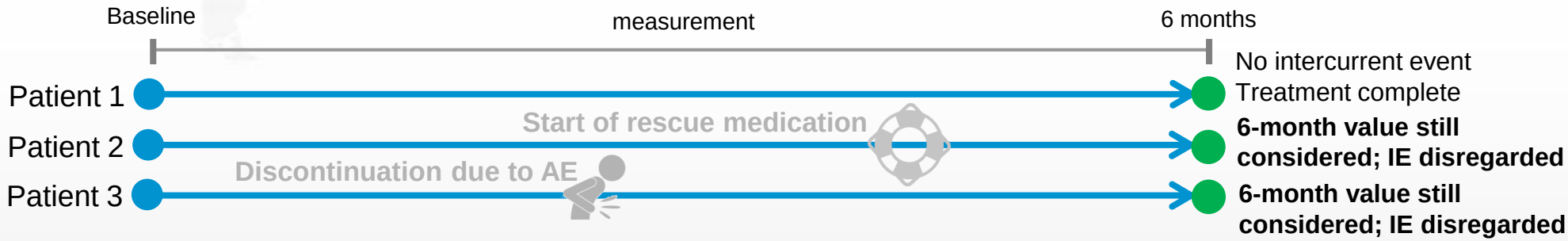
Returning to the example:

- **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…**

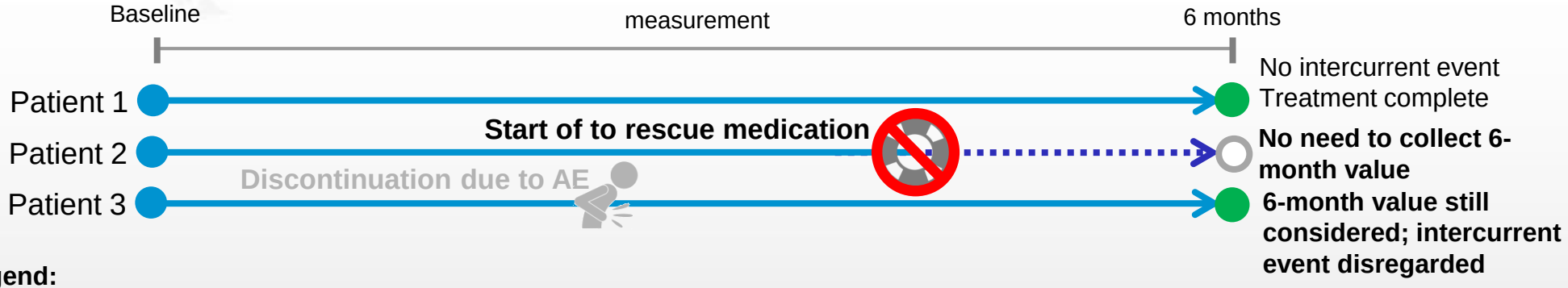


Legend:

- 6-month value has been collected
- Part of patient time course considered
- Intercurrent events (in grey when disregarded)
- IE Intercurrent event

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…**



Legend:

- 6-month value has been collected
- No need to collect 6-month value
- Part of patient time course considered
- Part of patient time course not observed and needs to be imputed/predicted
- Intercurrent event hypothetically not present. Time of intercurrent event marks the end of data collection.
- Intercurrent event (in grey when disregarded)

Multiple intercurrent events

- The definition of a clinically meaningful estimand needs to encompass **all intercurrent events that are likely to occur** and are **clinically relevant** in a given clinical trial setting.
- The description of the treatment effect being targeted cannot be fully understood without considering how to address the intercurrent events in the estimand. Taking into account intercurrent events is equally important for the choices made about the design, conduct and statistical analysis.
- Considering the five strategies discussed above, **all possible combinations of strategies** for two types of intercurrent events can be considered, although not all combinations will be **clinically relevant**.

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.

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Module 2

A.3.1. Description
A.3.2 Strategies for addressing intercurrent events
A.3.3 Construction of estimands

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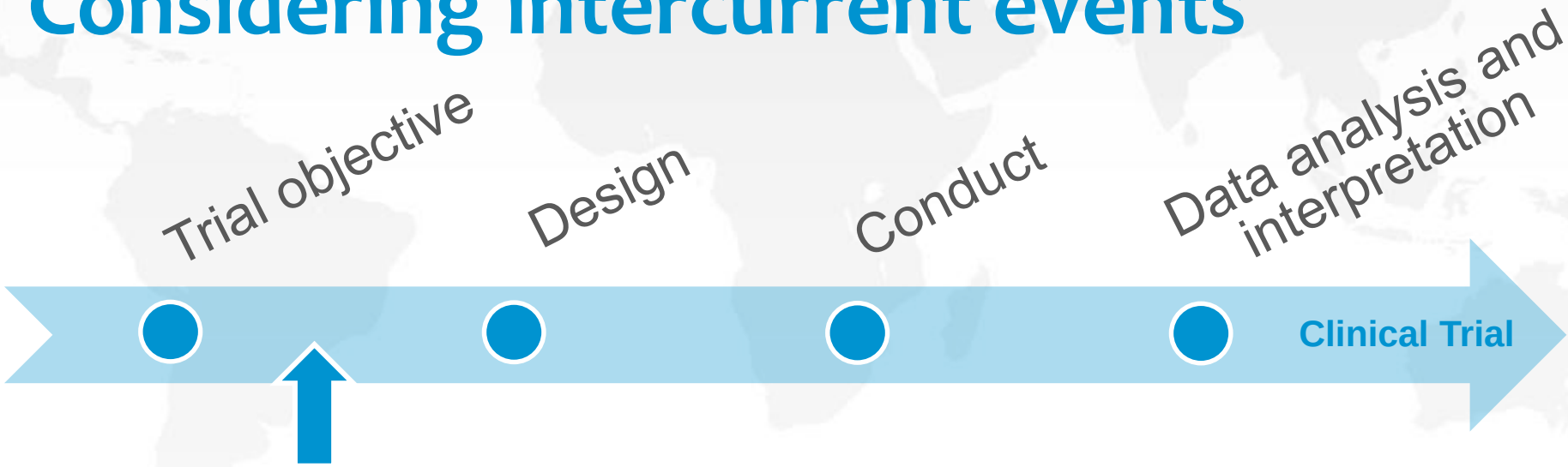
Module 2

A.3.3 Construction of estimands

A.3.3.1 General considerations

Considering intercurrent events

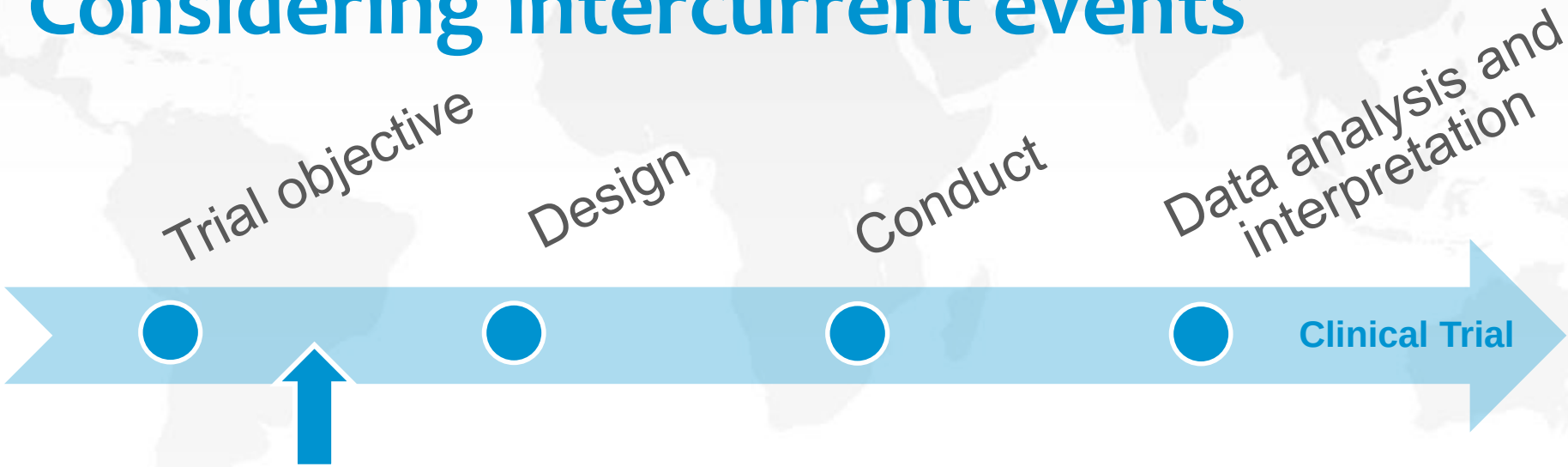


Each intercurrent event that may occur in the clinical trial and that will affect the interpretation of the results of the trial needs to be considered explicitly in the construction of the estimand.

This will…

- Unambiguously describe the treatment effect of interest;
- Promote the relevance of the treatment effect described to patients and physicians.

Considering intercurrent events

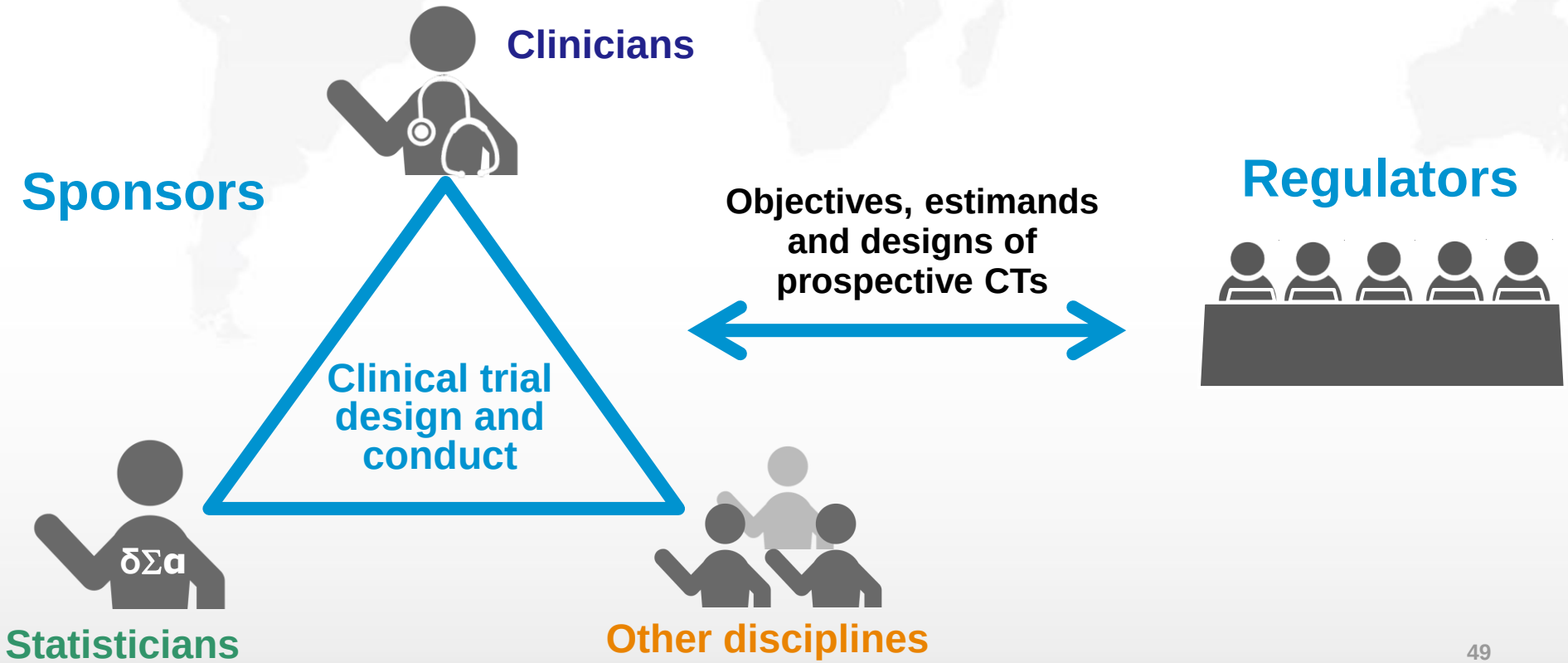


But…

- It's not always possible to foresee every relevant kind of 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

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



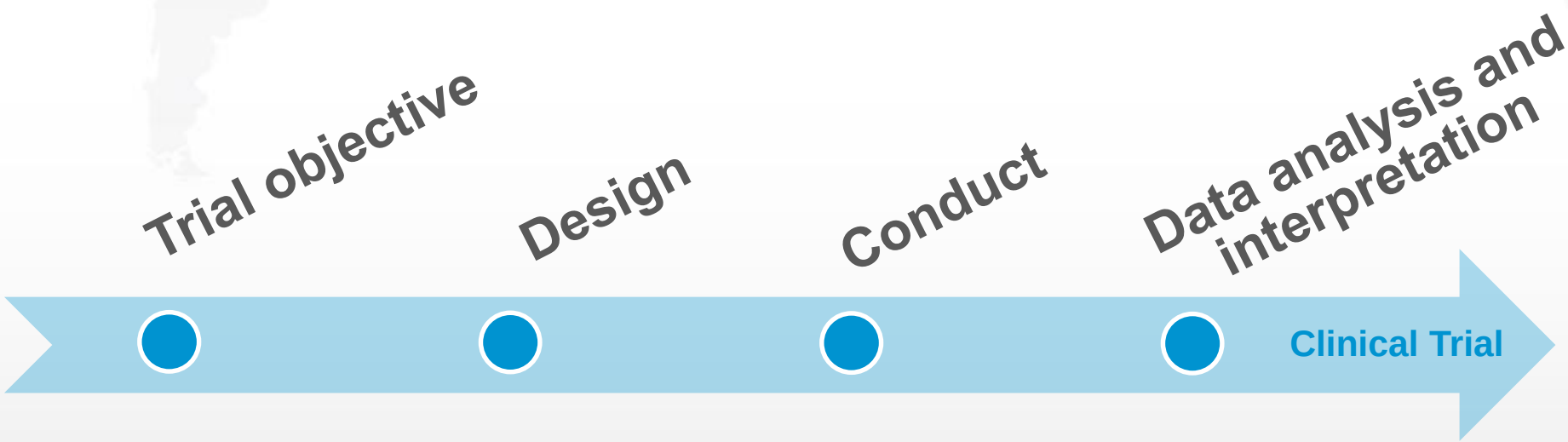
CTs: Clinical Trials

Construction of an estimand

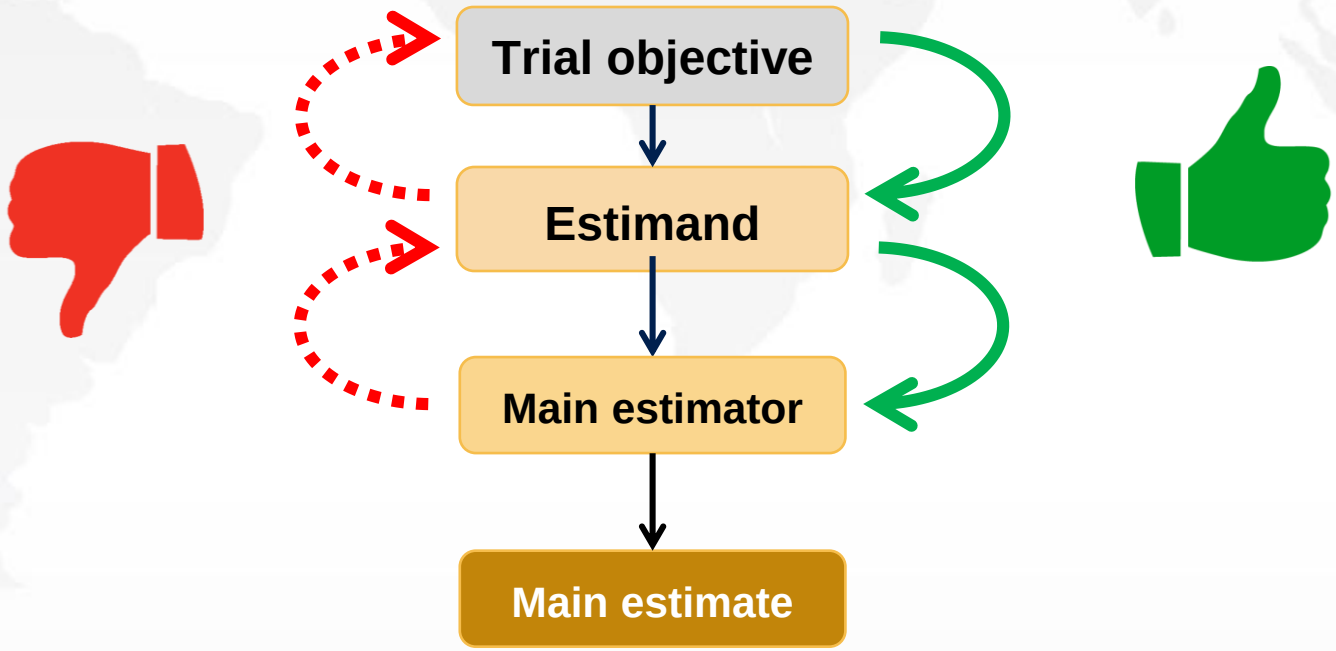
The construction of an estimand should be:

- Consequent to the trial objectives and should **precede choices** relating to **data collection** and **analytic approaches**; ✓
- **Clinically interpretable**, in terms of the population and endpoint, but also in terms of the strategies to account for intercurrent events and, finally, the summary measure; ✓
- Duly justified **considering the therapeutic setting** and the treatment goals of the intervention, from which the key scientific questions of interest can be derived. ✓

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



Construction of an estimand: How do we do it?



- Where significant issues exist to derive a reliable estimate for a particular estimand, the trial objectives need to be re-considered from top-down to main estimator (**green** arrows). The main estimator should never define the trial objective from bottom-up (**red** arrows).

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Module 2

A.3.3 Construction of estimands

A.3.3.2. Considerations of Therapeutic and Experimental Context

Important to keep in mind…

- The aim of the EWG was to develop and present a framework to facilitate these important discussions and not to give therapy-area specific recommendations.
- The points raised on subsequent slides are for reflection and are not designed to influence the preferred choice of strategy.

What can influence the construction of the estimand?

- **Disease setting:**
  - Are alternative treatment options available?
    - E.g. for glycaemic control in Type II diabetes mellitus multiple therapies are licensed.
  - Can individual response to treatment be monitored over time?
    - E.g. in hypertension, blood pressure is monitored frequently to assess response to treatment, inadequate response would be detected in a timely manner.
- **Aim of treatment:**
  - Controlling symptoms?
    - E.g. pain control in the treatment of migraine.
  - Modifying the course of disease or prevention of disease?
    - E.g. delay to the onset of dementia in prodromal Alzheimer's disease.

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 alternative strategies might be considered of greater clinical interest;
  - No other estimators can support a reliable estimate or robust inference.
- Treatment policy strategies 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.

Notes about the composite strategy

The treatment fails: patient considered as non-responder
No need to collect data after use of rescue medication

- **Example:** select a binary variable.
  - Response is based on a predefined threshold of change in score in the absence of the intercurrent event.
  - Patients who experience the intercurrent event (rescue medication in this case) will be considered non-responders.
- This dichotomisation of continuous scores would result in a different variable, and thus **a different estimand**.

Notes about the hypothetical strategy

No need to collect the end point value
Part of patient time course not observed and imputed/predicted

- Define the scientific question of interest based on the effect if rescue medication had not been available.
- The **hypothetical conditions** described must therefore be justified for the quantification of an interpretable treatment effect that is **relevant to the use of the medicine in clinical practice**.
- If the intercurrent event also depends on the **reason for the event** occurring, both event and reason have to be defined more precisely and recorded accurately in the clinical trial.

The experimental situation should always be considered!

In particular, the choice of the control arm might influence the manner in which rescue or other concomitant medications are permitted in the trial.

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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 analyses

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Draft (Step 2) guideline 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

June 2018

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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 choice of the estimand** or estimands that reflect the **primary trial objectives** and which will form the basis to establish whether those objectives have been met.
- **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

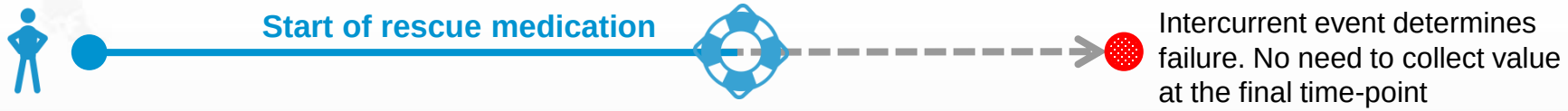
- The agreed **estimand dictates the data that need to be collected** during the trial.
- **Different estimands** might have **different requirements** regarding data collection.
- Each trial is likely to have **multiple estimands**, which means that data collection should be determined by the **need to address them all.**

The amount of patient withdrawals from the study doesn't 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**.

Design Options

- 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 dialogues with regulators may be necessary.

Other important aspects

- A **precise description of the estimand(s)** of interest should inform **sample size calculations**.
- For **summarising data 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** or the use of external control groups for the **interpretation of single-arm trials**.
- A trial may have **multiple objectives translated into multiple estimands**.
  - The multiplicity adjustments 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

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Draft (Step 2) guideline ICH E9(R1)

Estimands and Sensitivity Analysis in Clinical Trials

Training module 2.5: Impact on trial analysis

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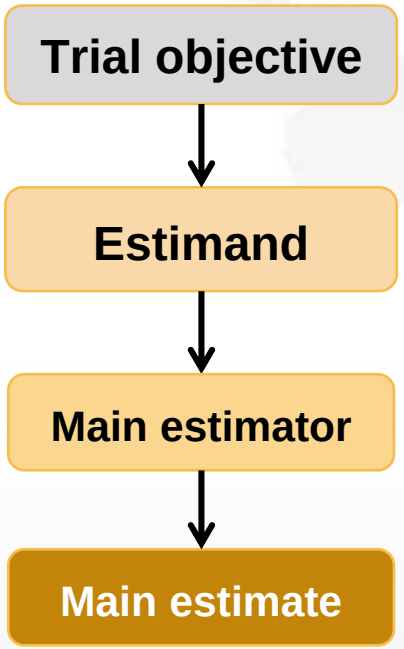
ICH E9(R1) – Table of Contents

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. 👎



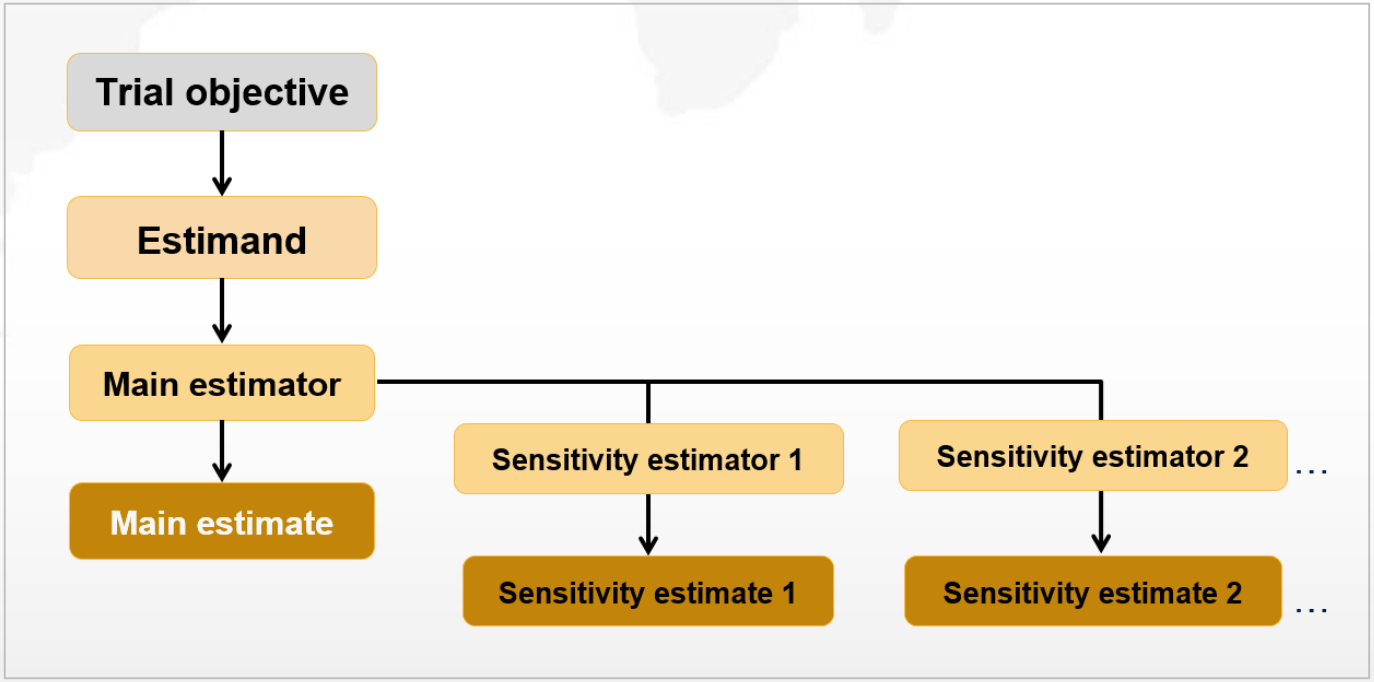
MMRM: Mixed Models for Repeated Measures
MAR: Missing At Random

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 to address missing data or to replace observed data (as required for estimation in the hypothetical strategy).

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.



Sensitivity analysis

Sensitivity analysis Is a series of analyses targeting the same estimand, with differing assumptions 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) Draft 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**: the relevance of these assessments will be determined by the strategy selected.
- 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) Draft 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**, assessments scheduled after the use of rescue medication **might not be required** for estimation.
- **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**.
- **One or more analyses**, focused on the same estimand, should then be **pre-specified** to investigate the impact of deviations from these assumptions.
- **Missing data** require particular attention in a sensitivity analysis because the assumptions underlying any method may be **hard to justify** fully and may be **impossible to test**.

Supplementary analysis

- If the **estimate** corresponding to a given estimator, and associated inference, is shown to be **robust** through sensitivity analysis, then the **interpretation of trial results** should focus on the main estimator for each selected estimand.
- **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 might **target different estimands**, or target the **same estimand based on a different analytical approach**.

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) Draft addendum

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.
- For example, investigating assumptions of normality associated with ANOVA would result in sensitivity analysis; analysing the dataset instead based on comparison of medians would be considered a supplementary analysis.

ANOVA: Analysis of variance

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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

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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Draft (Step 2) guideline ICH E9(R1)

Estimands and Sensitivity Analysis in Clinical Trials

Training module 2.6: Documenting estimands and sensitivity analysis

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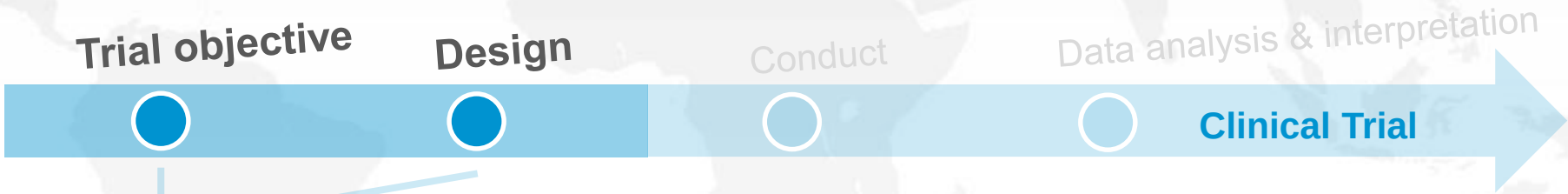
ICH E9(R1) – Table of Contents

Outline of Module 2.6

- Incorporating estimands in the writing of a trial protocol and statistical analysis plan
- Potential impact of ICH E9(R1) on study conduct
- Data analysis and interpretation

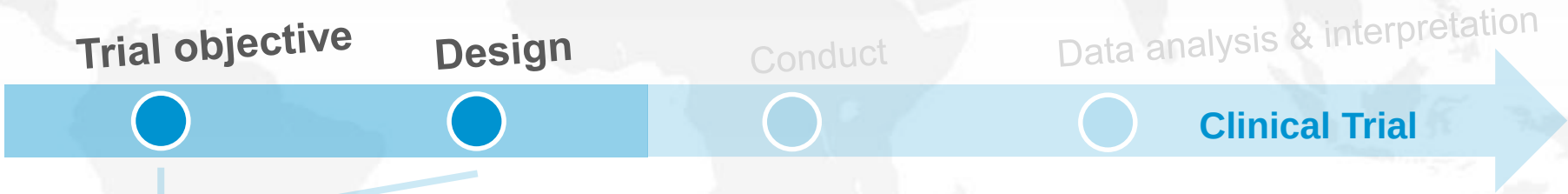
Incorporating estimands in protocol writing



Trial Protocol

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

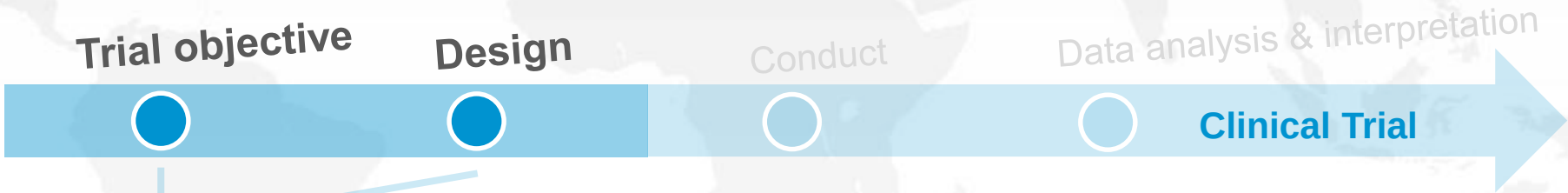
Incorporating estimands in protocol writing



Trial Protocol

- Estimands for **secondary trial objectives** (e.g. related to **secondary variables**) that are likely to support regulatory decisions should be **described properly**, 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**.
- It is not a regulatory requirement to document in detail an estimand for each exploratory question.

Incorporating estimands in protocol writing



Trial Protocol

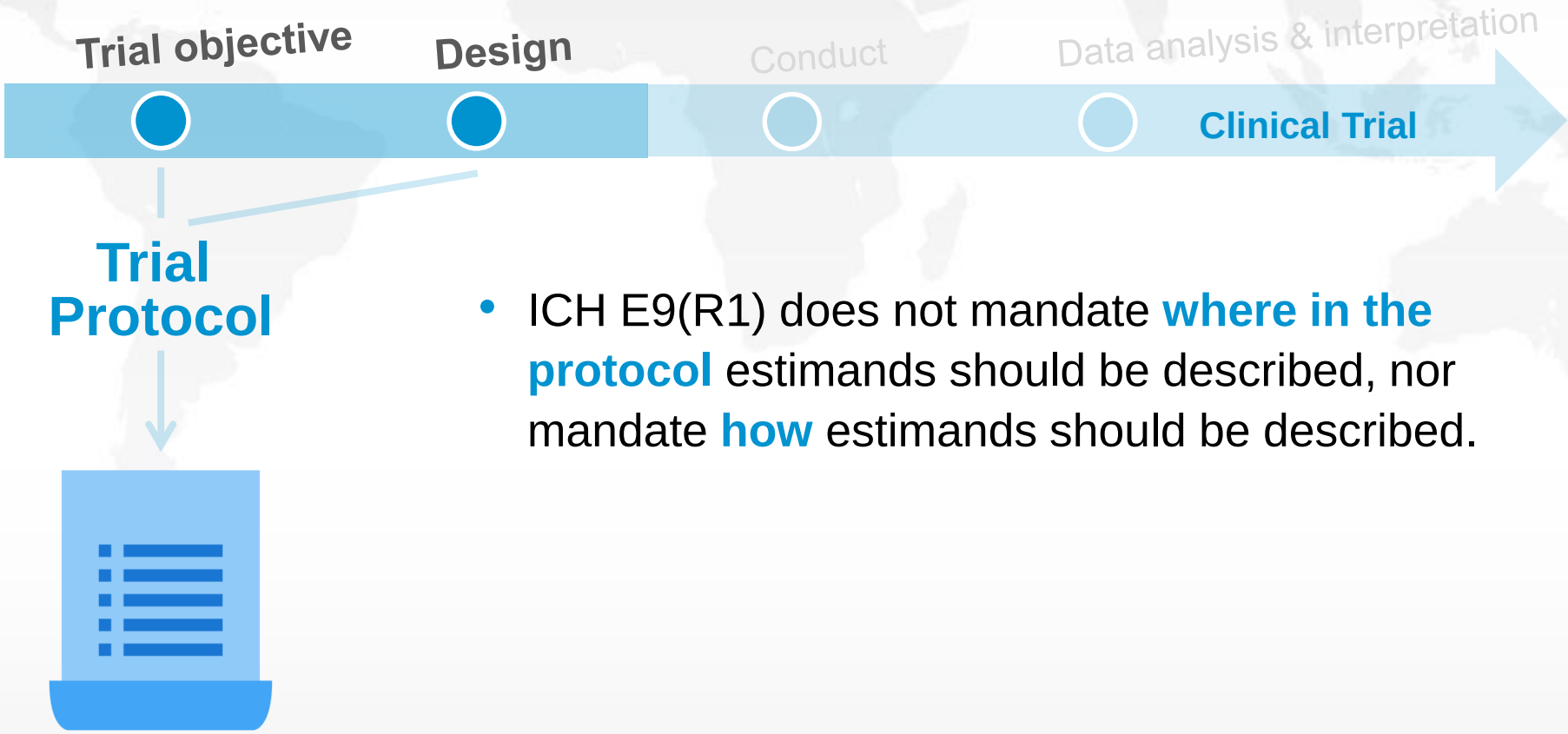
- Where **different scientific questions of interest** call for **materially different estimands**, it is recommended that these should be **fully documented**.

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

Incorporating estimands in protocol writing

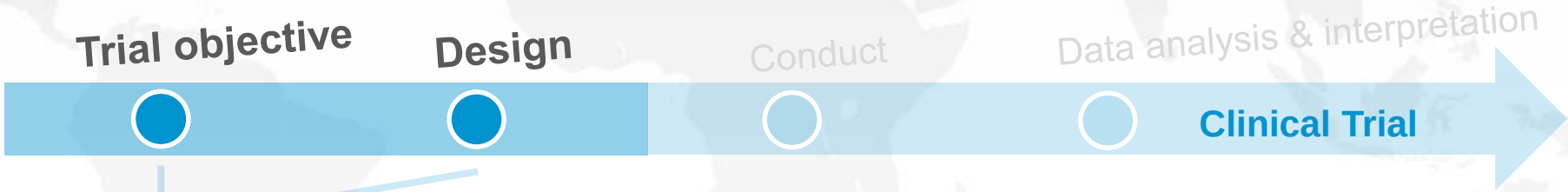
- The **trial analysis summarised in the protocol should be aligned with the primary estimand** with regards to (including but not limited to):
  - **Handling of intercurrent events**, for example:
    - Use of rescue medication;
    - Changes in permitted medications;
    - Switching treatments;
    - Discontinuing treatment;
    - Subject deaths.
  - The selection of subjects to be included in the analyses.
  - Multiplicity issues e.g. if there is more than one estimand.

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.

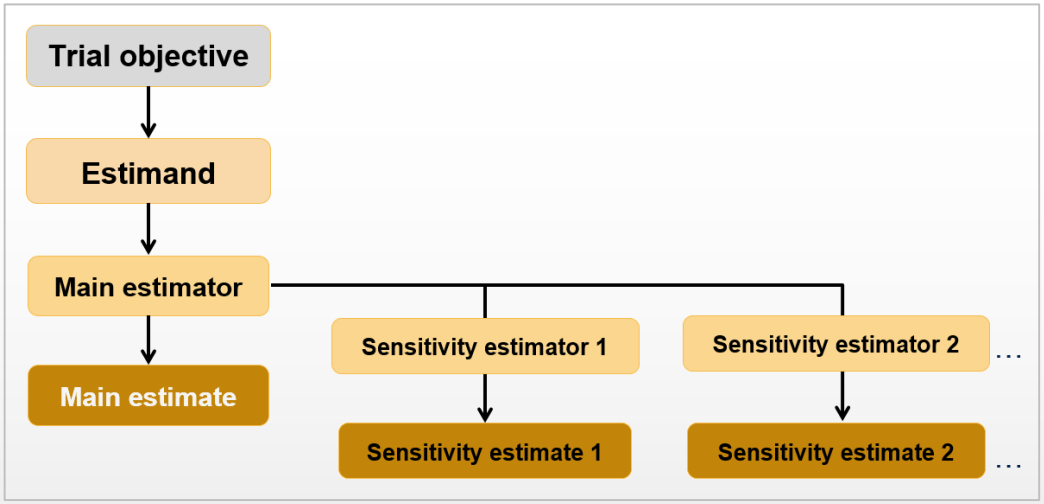
Incorporating estimands in the SAP



Trial Protocol

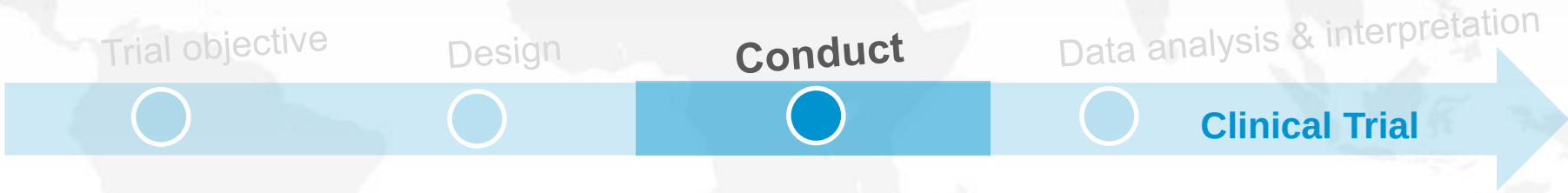
Statistical Analysis Plan

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



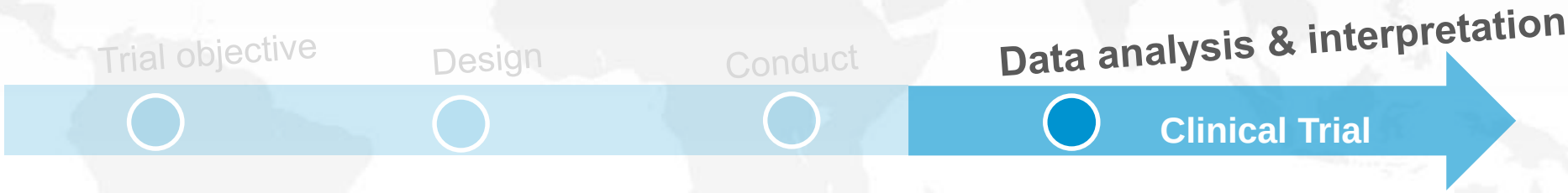
SAP: Statistical Analysis Plan

Potential impact on study conduct



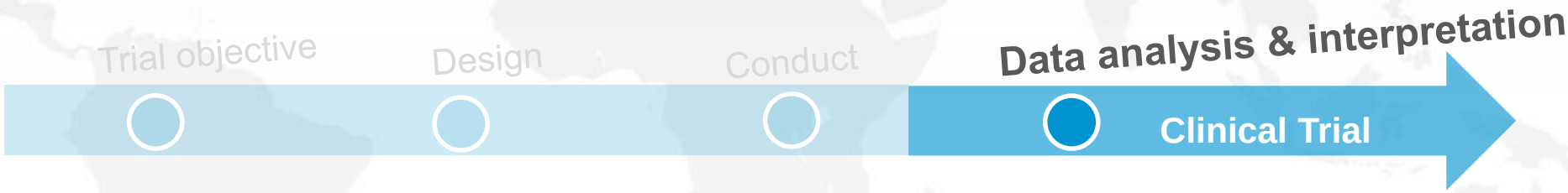
- The occurrence of anticipated intercurrent events should be **monitored during the study**.
- Estimands defined in the trial protocol could be subsequently **affected by issues arising during study conduct**.
- The impact of any **unanticipated intercurrent events** occurring and/or other study conduct issues possibly affecting the primary estimand should be evaluated.
- A **protocol amendment** could be considered depending on the nature and significance of such issues to the primary estimand.

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**.

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 in the analysis**;
  - explain the **impact on what the revised analysis estimates (i.e. the impact on the pre-specified estimand)**.
- Consultation with regulators to agree the preferred handling of intercurrent events not initially foreseen might be advisable.

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Next module:

3. Generic example

Draft (Step 2) guideline ICH E9(R1)

Estimands and Sensitivity Analysis in Clinical Trials

Training module 3: Generic Example

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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).

The current slide deck reflects the content on the Draft ICH E9(R1) addendum up to the time of its publication for public consultation. Content may be changed as a result of the consultation phase.

Legal Notice

Introduction note

These slides were produced as training material to accompany the Draft 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 and case studies 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

ICH
harmonisation for better health

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**
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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 therapeutic setting includes the disease or condition under study and, for example, the availability of other treatment options and the possibilities to monitor individual response to treatment.
- **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 the example, consider a variable measured monthly on a continuous scale (e.g. systolic blood pressure, SBP, after 6 months in hypertension).

SBP: Systolic blood pressure

A thinking process…

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

Intercurrent events Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation.

Intercurrent events definition, ICH E9(R1) Draft 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 that can occur in a clinical trial

2 Identify intercurrent events

- **Common intercurrent events**
  - Treatment discontinuation/non-adherence to treatment, perhaps identified as multiple separate intercurrent events distinguished by reason (e.g. treatment discontinuation due to lack of efficacy, due to toxicity,…);
  - Use of additional medication, perhaps distinguished by type and / or reason, e.g.:
    - rescue medication due to lack of efficacy; treatment switch; use of prohibited medication; change in background medication;
  - Death and other terminal events.

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

2 Identify intercurrent events

Example – Drug X

- **Examples of intercurrent events that might be foreseen**
  1. Treatment discontinuation/non-adherence to treatment.
  2. Use of additional medication (that will impact measurements of SBP).

SBP: Systolic blood pressure

A thinking process…

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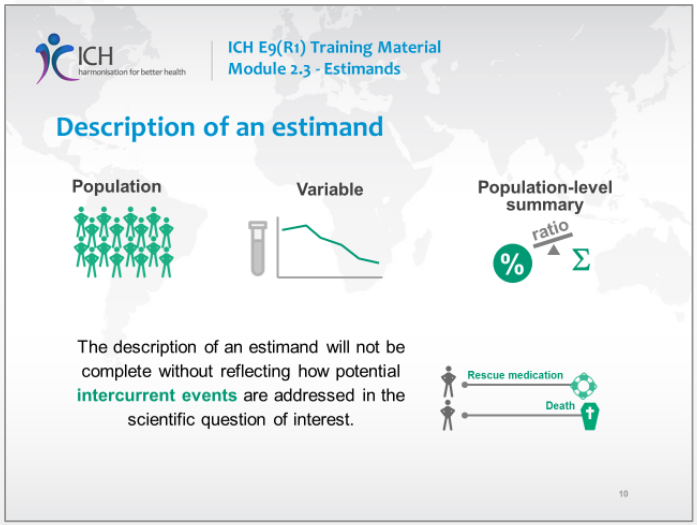
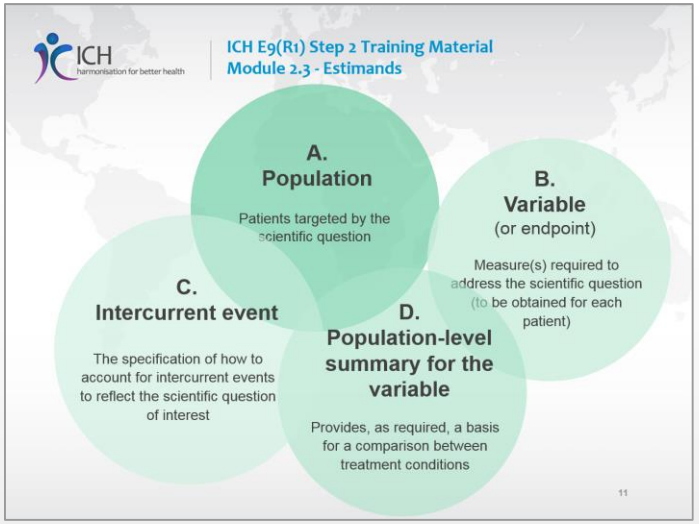
Check Module 2.3

③ Discuss strategies to address intercurrent events

- **Discuss…**
  - Consider different strategies to address these two intercurrent events (slides 19-21 and 22-24 respectively).
  - Reflect how to account for intercurrent events through the estimand attributes A-D (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 **scientific 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 **relevant for** sponsor, regulator and prescriber **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 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 (specified in attribute C).

SBP: Systolic blood pressure

③ Discuss strategies to address intercurrent events

Example – Drug X

2. **Composite:** for example, the treatment effect is established based on a composite variable combining a clinically meaningful change in SBP and continuation of treatment at month 6. Thus both lack of meaningful change and treatment discontinuation will be captured as unfavourable outcomes (specified, if using a composite variable, in attribute B).

3. **Hypothetical:** to investigate a treatment effect at month 6 if all patients continue with treatment (specified in attribute C).

SBP: Systolic blood pressure

③ Discuss strategies to address intercurrent events

Example – Drug X

4. **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 attribute A).

5. **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 attribute B).

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 treatment on SBP**.
- Intercurrent event (2) = **use of additional 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 medication. This strategy will capture both the effect of Drug X and the effect of additional medication (specified in attribute C).

SBP: Systolic blood pressure

③ Discuss strategies to address intercurrent events

Example – Drug X

2. **Composite:** for example, the treatment effect is established based on a composite variable indicating a clinically meaningful change obtained without the use of additional medication at month 6. This will capture both lack of meaningful change and the use of additional medication as unfavourable outcomes (specified, if using a composite variable, in attribute B).
3. **Hypothetical:** investigate the treatment effect at month 6 if additional medication would not be available to patients. This strategy aims to capture the effect of drug X without the effect of additional medication (specified in attribute C).

③ Discuss strategies to address intercurrent events

Example – Drug X

4. **Principal stratum:** to investigate the effect of treatment at month 6 in the stratum of the population who would not use additional medication on drug X (specified in attribute A).

5. **While on treatment:** to investigate the effect of treatment before the point at which the patient uses additional medication (specified in attribute B).

A thinking process…

1. Therapeutic setting and intent of treatment determining a trial objective
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4. **Construct the estimand(s)**
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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/non-adherence to treatment → **Treatment policy (specified in attribute C)**.
  - Use of additional or alternative medication that affects SBP → **Hypothetical (specified in attribute C)**.

* 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 (4 attributes):

A. **Population:** defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval.

B. **Endpoint:** change from baseline to month 6 in SBP.

C. **How to account for intercurrent events:** if additional medication was not available to patients prior to month 6 and regardless of whether or not the patient continue with treatment

D. **Population-level summary:** difference in variable 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 between treatment conditions in the target patient population for the change from baseline to month 6 in SBP, if additional medication was not available to patients prior to month 6 and regardless of whether or not the patient continues with treatment.

* 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/non-adherence to treatment → **Treatment policy (specified in attribute C)**.
  - Use of additional or alternative medication that affects SBP → **Composite (specified in attribute B)**.

* 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 (4 attributes):

A. **Population:** defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval.

B. **Endpoint:** binary response variable indicating a successful response if a clinically meaningful change from baseline to month 6 in SBP is obtained without the use of additional medication

C. **How to account for intercurrent events:** regardless of whether or not the patient continue with treatment.

D. **Population-level summary:** difference in response 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 response proportions between treatment conditions in the target patient population in successful responses at month 6 in SBP without use of additional medication, regardless of whether or not the patient continues with treatment.

* 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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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 treatment effect can be derived that is reliable for decision making.**

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

A balance might need to be struck between an estimand of **greater clinical relevance** estimated with an analytical approach that requires numerous assumptions, and an estimand of **less clinical relevance** that can be estimated with an analytical approach requiring few assumptions. This will 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.
- **Consider the data that would need to be collected,** e.g. for the use of additional medication:
  - for a treatment-policy strategy it should be planned that **all measurements of SBP regardless of use of additional medication are collected** throughout the trial;
  - for a hypothetical strategy **measurements of SBP after the use of additional medication would not need to be collected** (for this estimand, but might be required for others).

SBP: Systolic blood pressure

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

Example – Drug X

- **Consider whether an estimate of treatment effect can be derived that is reliable for decision making,** e.g. for the use of additional 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** measurements of SBP after the use of additional medication are not relevant and values must be imputed or predicted, relying 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 treatment effect can be derived that is reliable for decision making,** e.g. for the use of additional medication (continued):
  - for a **principal stratum strategy** estimation of a treatment effect will be confounded unless the subjects within that stratum can be identified before randomisation. Otherwise, estimation will rely on model assumptions that will require extensive sensitivity analysis.
  - for a **while on treatment strategy** estimation of a treatment effect will require strong assumptions when the occurrence and timing of an intercurrent event is related to treatment and will require extensive sensitivity analysis.

- **The extent of 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 between treatment conditions in the target patient population for the change from baseline to month 6 in SBP, if additional medication was not available to patients prior to month 6 and regardless of whether or not the patient continues with treatment.
- Discuss and select **a method for estimation*** that is **aligned** to the estimand:
  - e.g. ANCOVA with imputation of the measurements after the patient uses additional medication, perhaps based on data in the placebo group.

SBP: Systolic blood pressure
ANCOVA: Analysis of covariance

* This is not an indication of regulatory preference or policy

A thinking process…

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Check Module 2.5

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

Sensitivity analysis Is a series of analyses targeting the same estimand, with differing assumptions 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) Draft addendum

- 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 between treatment conditions in the target patient population for the change from baseline to month 6 in SBP, regardless of whether or not patients continue with treatment, if additional medication was not available.
- **Method for estimation* (slide 38):** e.g. ANCOVA with imputation of the measurements after the patient uses additional medication, perhaps based on data from the placebo group.
- **Sensitivity analysis can be planned based on alternative methods for predicting / imputing response after use of additional medication.**

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 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.

ANCOVA: Analysis of covariance

A thinking process…

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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

- The ICH E9(R1) Step 2 document does not specify the format of the estimand specification.
  - It is not required that attributes A-D are separately specified.
  - It is required that a reviewer can identify intercurrent events and the strategies selected, and hence a precise estimand description reflecting the scientific question of interest.
- **Estimands for all trial objectives that are likely to support regulatory decisions 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 feasible given the timelines of the study) if the estimand is to be revised, ensuring that alignment with trial design and statistical analysis is maintained.

- If omission of an important intercurrent event is **noted only at the time of analysis**, 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 analysis should be presented and discussed with reference to the estimand.
- The occurrence and timing 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) Step 2 training material slide decks