



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
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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.

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Introduction note

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

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

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

Training modules

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

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Module 2.3

Module 2.5

Outline of Module 2.3

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

Module 2.3

A.3.1. Intercurrent Events to be Reflected in the Clinical Question of Interest

A.3.2 Strategies for addressing
intercurrent events when Defining the
Clinical Question of Interest

A.3.3 Estimand Attributes

A.3.4. Considerations for Constructing an
Estimand

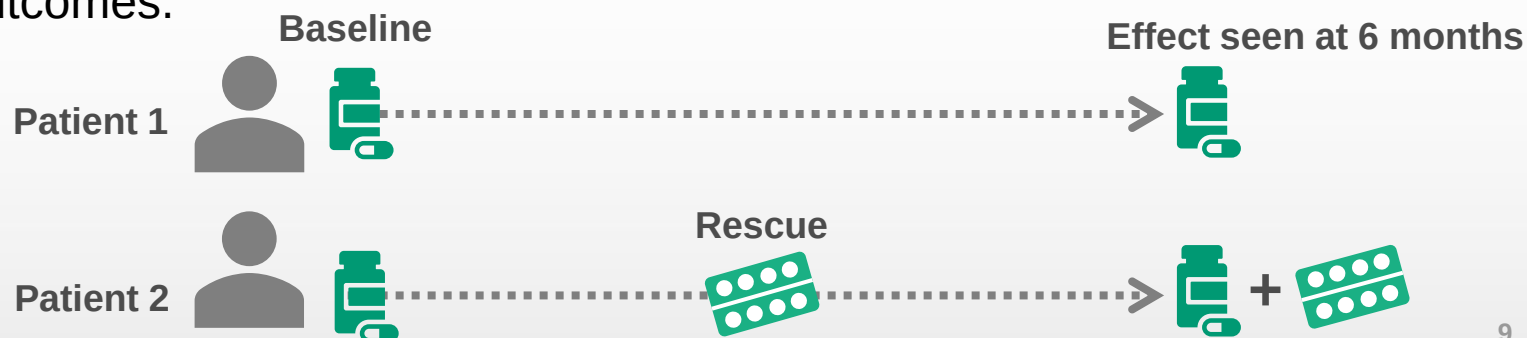
Quantification of treatment effect

A central question for drug development and licensing...

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

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

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



Quantification of treatment effect

A central question for drug development and licensing...

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

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

- **An estimand defines in detail what needs to be estimated to address a specific scientific question of interest, posed by the trial objective.**
 - It summarises at a population level what the outcome would be in the same patients under different treatment conditions being compared.
 - It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

Description of an Estimand

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



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

Intercurrent events

Intercurrent events: Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

Intercurrent events definition, ICH E9(R1) addendum



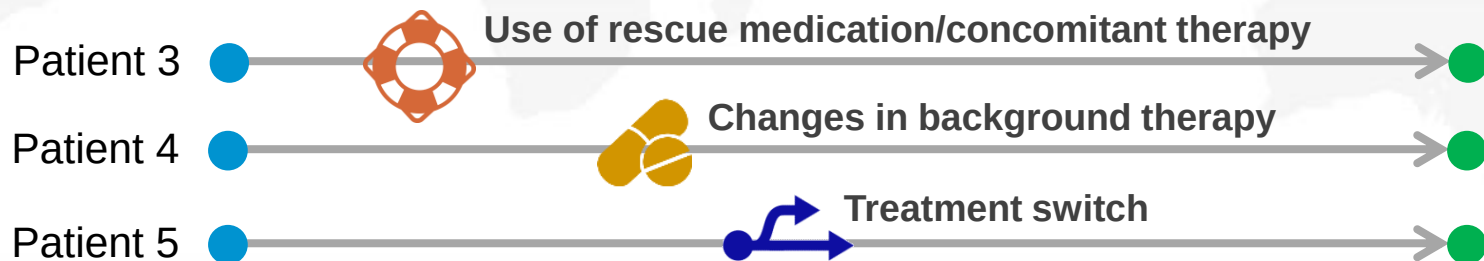
Unlike missing data, intercurrent events are not to be thought of as a drawback to be avoided in clinical trials, as they can also occur in clinical practice!

Intercurrent events - examples

Treatment discontinuation



Additional / alternative treatment



Terminal events



Randomisation

TIMELINE

Data collection for the variable

Intercurrent events - examples

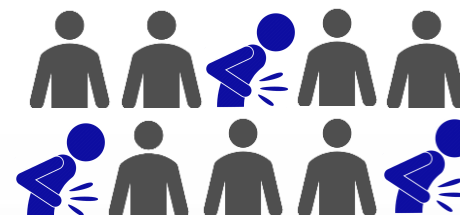
- Some **clinical events** can also be **intercurrent events** when their **occurrence (or non-occurrence) defines a principal stratum** of interest.
- Examples may include:

Tumour shrinkage
(= objective response)



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

Occurrence of infection



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

Need for precision when describing IEs

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

Intercurrent events $\neq$ missing data

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

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

Missing data definition, ICH E9(R1) addendum

Module 2.3

A.3.1. Intercurrent Events to be Reflected in the Clinical Question of Interest

A.3.2 Strategies for addressing intercurrent events when Defining the Clinical Question of Interest

A.3.3 Estimand Attributes

A.3.4. Considerations for Constructing an Estimand

Strategies for addressing intercurrent events

- The following slides will describe possible strategies to address intercurrent events.
- The strategies are chosen to **reflect the clinical question of interest** for **each intercurrent event**.
 - Different strategies will often be used for different intercurrent events within the same estimand.
 - The names of the strategies are just for ease of reference. What is essential is to make clear what the strategy for each intercurrent event is, once the estimand is constructed.
 - The relevance of each strategy will depend on the **therapeutic and experimental context**.
 - Not all strategies will be equally acceptable for regulatory decision making!

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

Let's take an example...



Drug X

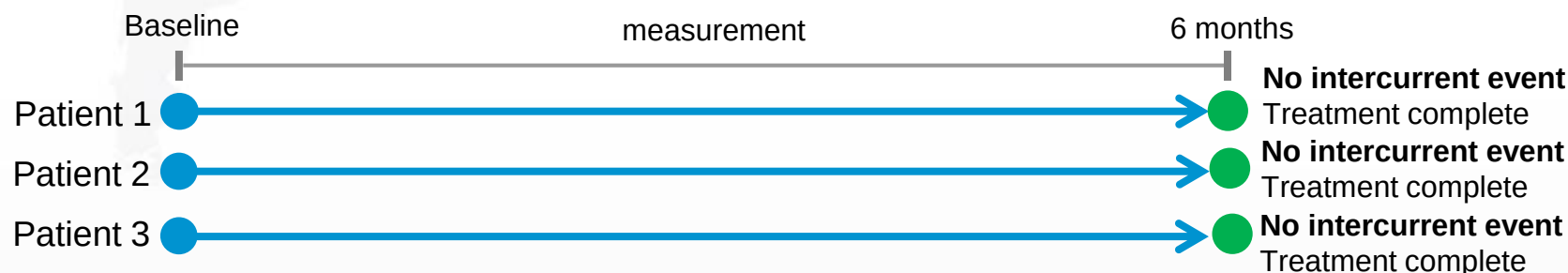


Indicated for a chronic, non-life-threatening disease

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

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

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



Legend:

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

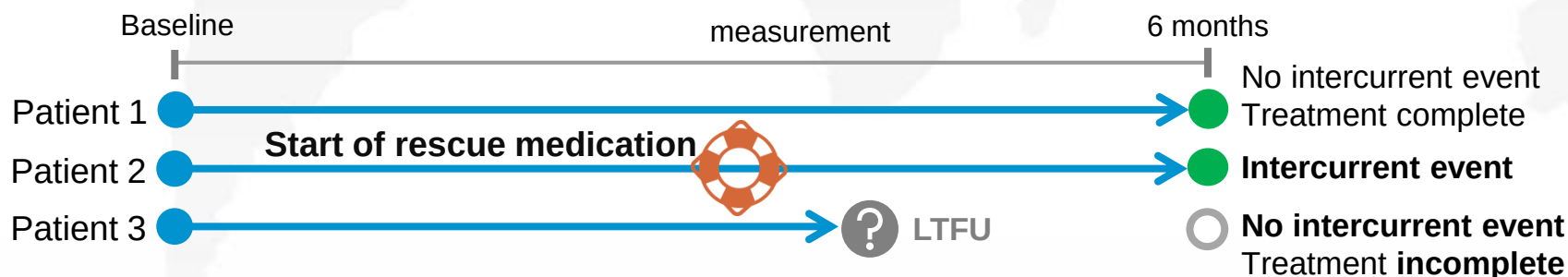
**Now assuming that there
are intercurrent events...**

1. Treatment policy strategy

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

1. Treatment policy strategy - example

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



- **Applying the treatment policy strategy**



Legend:

- 6-month value has been collected
- 6-month value has not been collected, data are missing
- ⊙ LTFU - Patient lost to follow-up

- ⊙ Intercurrent event - in grey when disregarded
- Part of patient time course considered
- ... Part of patient time course not observed and needs to be imputed/predicted

2. Hypothetical strategies

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

2. Hypothetical strategies

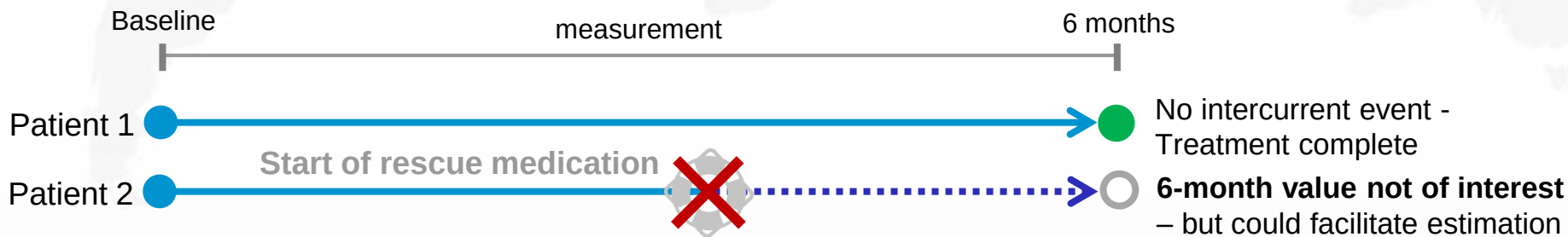
Important to keep in mind...



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

2. Hypothetical strategies - example

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



Legend:

-  6-month value has been collected and outcome is positive
-  No need to collect 6-month value
-  Part of patient time course considered

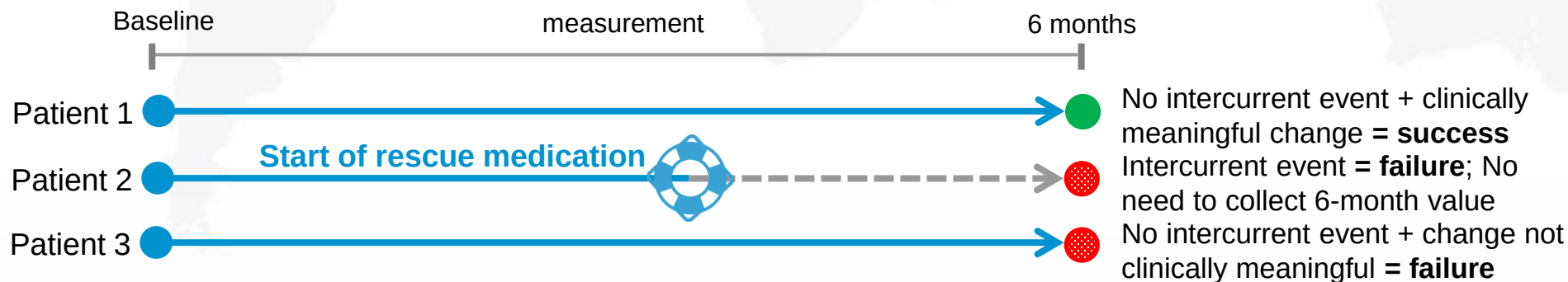
-  Part of patient time course not observed, may need to be imputed/predicted
-  Intercurrent event hypothetically not present. Time of intercurrent event marks the end of data collection unless it facilitates estimation.

3. Composite strategies

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

3. Composite strategies - example

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



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

Legend:

-  6-month value has been collected and outcome is positive
-  Outcome is negative regardless of having been collected
-  Part of patient time course considered

-  Part of patient time course not considered.
-  Intercurrent event as part of the composite variable. Time of intercurrent event marks the end of data collection.

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



-  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.

4. While on treatment strategies

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

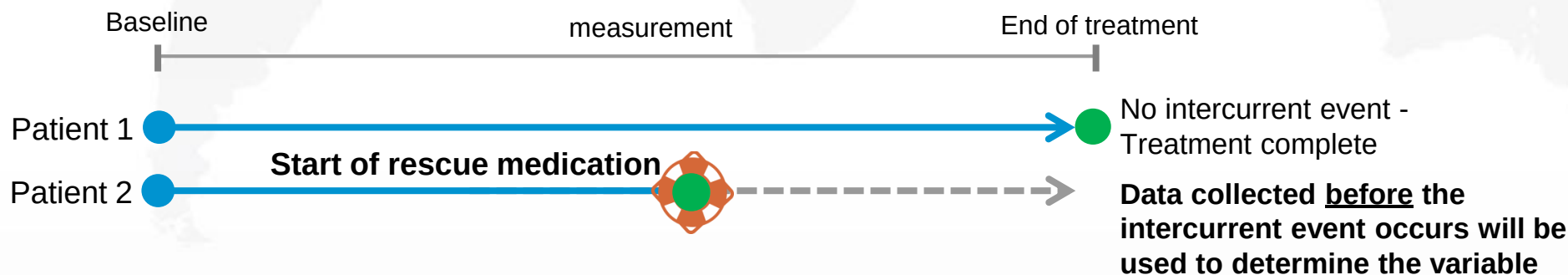
4. While on treatment strategies

o For example (cont.):

- subjects might discontinue treatment, and in some circumstances it will be of interest to assess the risk of an adverse drug reaction during the period of adherence to treatment.
- The while on treatment strategies can **impact on the definition of the endpoint**, for example, by restricting the observation time of interest to the period between baseline and the occurrence of the intercurrent event.
- The terminology used in the strategy will depend on the intercurrent event of interest: e.g. “while on treatment”, “while alive”, etc.
- Particular care is required if the occurrence of the intercurrent event **differs between the treatments being compared**

4. While on treatment strategies - example

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



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

Legend:

● End point value has been collected

— Part of patient time course considered

— Part of patient time course not considered

● Time of intercurrent event marks end of data collection (merged with green dot).

5. Principal stratum strategies

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

5. Principal stratum strategies

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

5. Principal stratum strategies - example

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

Patients fall into exactly one of these four strata:

- **S₀₀**: stratum of patients who require rescue medication independently of treatment or placebo;
- **S₀₁**: stratum of patients who require rescue medication on placebo and do not require it on treatment;
- **S₁₀**: stratum of patients who require rescue medication on treatment and do not require it on placebo;
- **S₁₁**: 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	S₀₀	S₀₁
	No rescue medication	S₁₀	S₁₁

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

Multiple intercurrent events – example

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

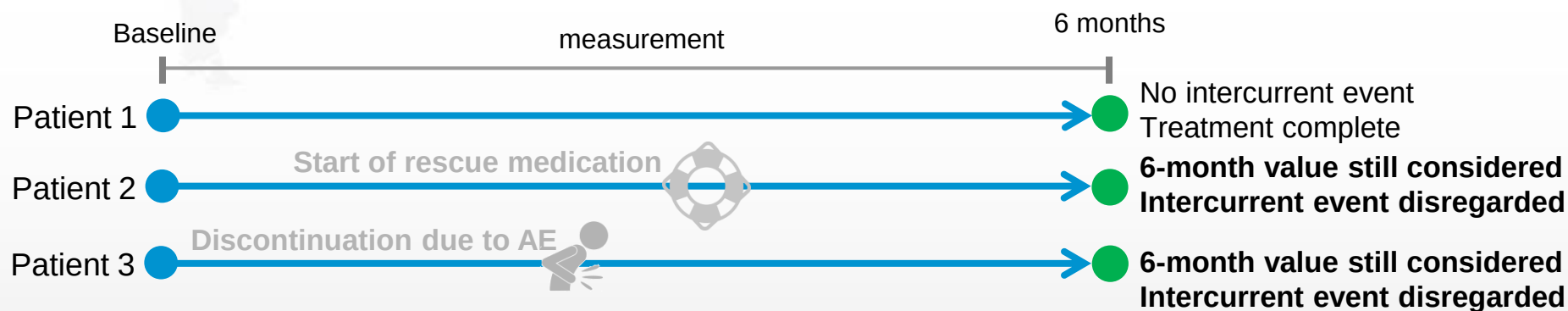
Returning to the example:

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

Second
intercurrent event

Multiple intercurrent events – example

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



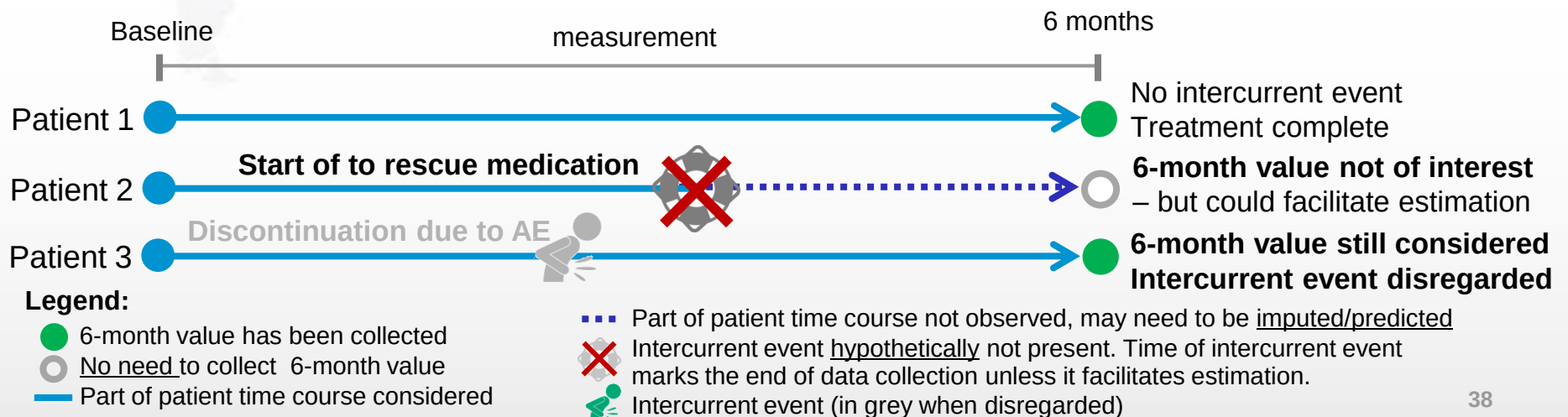
Legend:

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

  Intercurrent events (in grey when disregarded)

Multiple intercurrent events – example

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



Further considerations on strategies



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



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



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

Module 2.3

A.3.1. Intercurrent Events to be Reflected in the Clinical Question of Interest

A.3.2 Strategies for addressing intercurrent events when Defining the Clinical Question of Interest

A.3.3 Estimand Attributes

A.3.4. Considerations for Constructing an Estimand

Estimand attributes

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

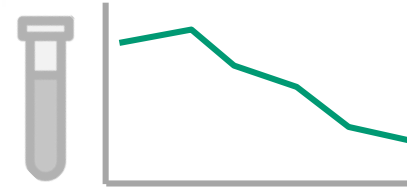
Treatment



Population



Variable



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

Other intercurrent events (not included in other attributes)



Population-level summary



Treatment

The treatment condition of interest, and treatment to be compared

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

Population

Patients targeted by the clinical question

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

Variable (or endpoint)

To be obtained for each patient in order to address the clinical question

*May include whether the patient experiences an IE – **Composite, While on Treatment***

Other intercurrent events

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

Population-level summary for the variable

Provides a basis for comparison between treatment conditions

Treatment

The treatment condition of interest, and treatment to be compared

May include whether the treatments are handled – *policy, hypothetical*

Population

Patients targeted by the clinical question

Can be defined by a *population*

Variable (or endpoint)

To be obtained for each patient in order to address the clinical question

May include whether the patient experiences an IE – *disposition, While on Treatment*

All these attributes can be combined to describe the
estimand

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

variable

Provides a basis for comparison between treatment conditions

Estimand attributes

Treatment

The treatment condition of interest, and treatment to be compared

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



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

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

Estimand attributes

Population

Patients targeted by the
clinical question

*Can be defined by a
principal stratum*



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

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

Estimand attributes

Variable (or endpoint)

To be obtained for each patient in order to address the clinical question

May include whether the patient experiences an IE –
Composite, While on Treatment



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

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

Estimand attributes

Other intercurrent events

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



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

Estimand attributes

Population-level summary for the variable

Provides a basis for comparison between treatment conditions.



Population-level summary for the variable

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

ICH E9(R1) Training Material Module 2.3 - Estimands

Study objectives

Clinical question of interest with clear study objectives

Intercurrent events

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

Strategies

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

Attributes

Treatment

Population

**Variable
(or endpoint)**

**Other
intercurrent
events**

**Population-
level
summary**

ESTIMAND

Module 2.3

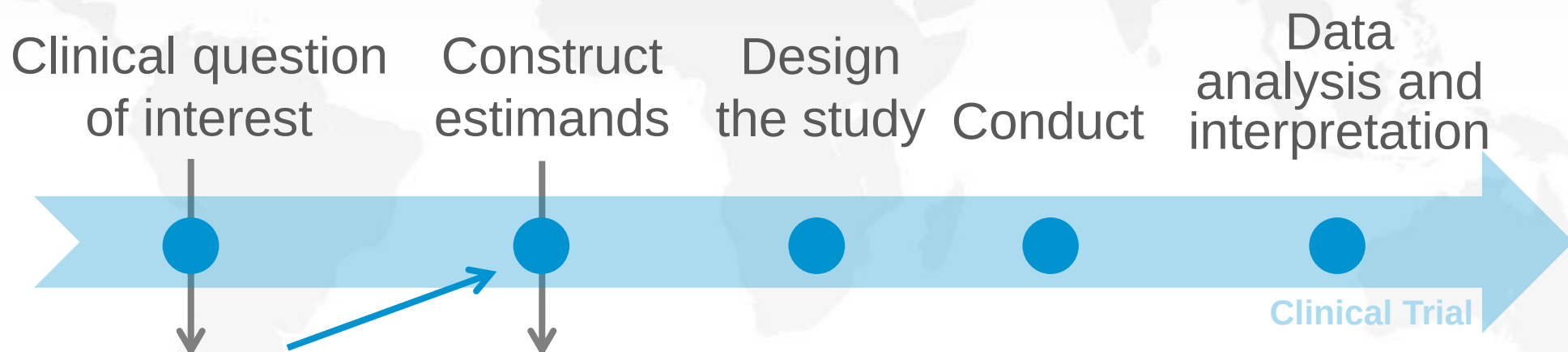
A.3.1. Intercurrent Events to be Reflected in the Clinical Question of Interest

A.3.2 Strategies for addressing intercurrent events when Defining the Clinical Question of Interest

A.3.3 Estimand Attributes

A.3.4. Considerations for Constructing an Estimand

Considering intercurrent events



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

Need to consider:

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

Clear and unambiguous definition of the target of estimation = estimand

Construction of an estimand

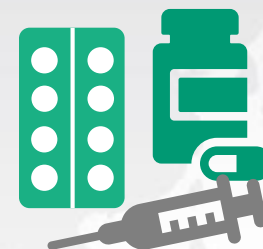
Clinical relevance in the therapeutic setting

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

Considerations include:

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





Construction of an estimand

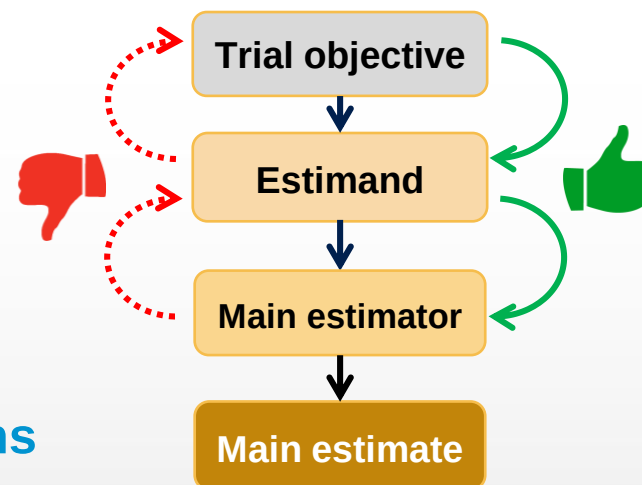
Clear understanding of the treatment

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

Construction of an estimand

Deriving a reliable estimate for decision making

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





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

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

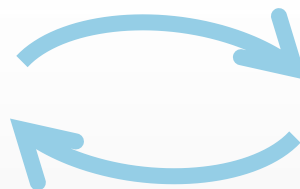
Construction of an estimand

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

Sponsors



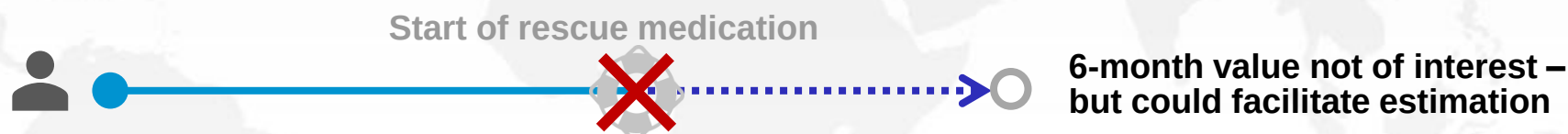
Trial objectives,
estimands and
design



Regulators

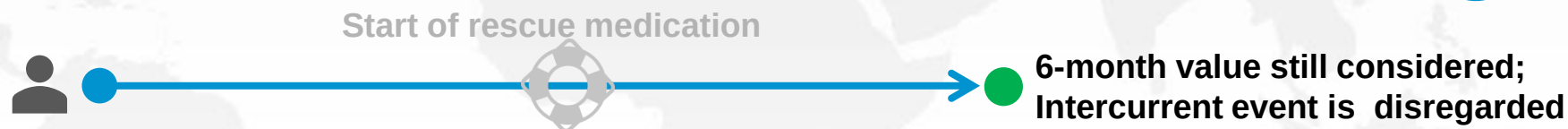


Notes about the hypothetical strategy



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

Notes about the treatment policy strategy



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

Estimands for non-inferiority and equivalence trials

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

Next module:

2.4. Impact on trial design and conduct

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