

Handling Intercurrent Events in Safety Analysis

Bringing safety evaluation in clinical development to the future

Estimands in Safety Analytics Project
Topic 2

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Katarina is working on this slid

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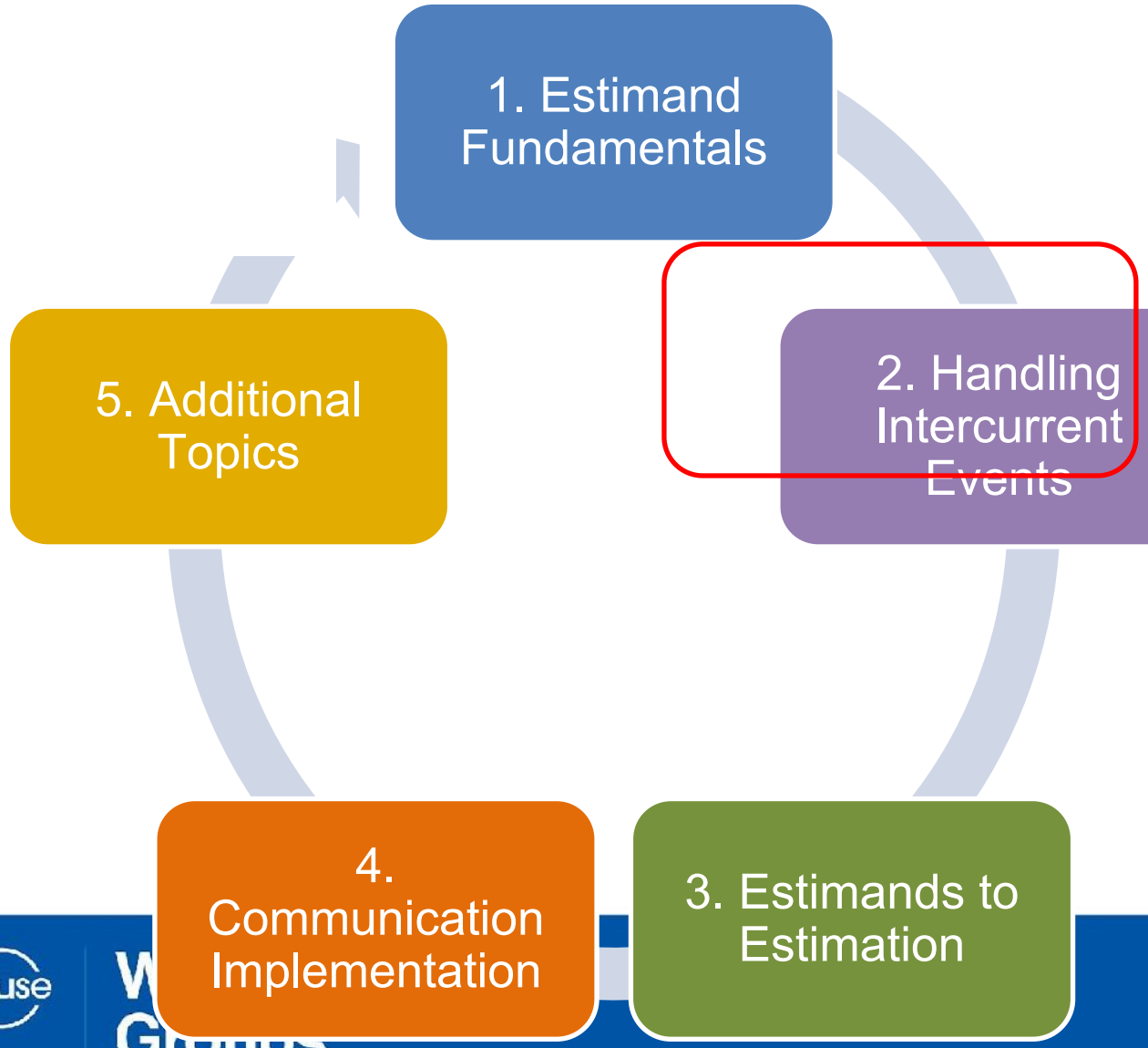
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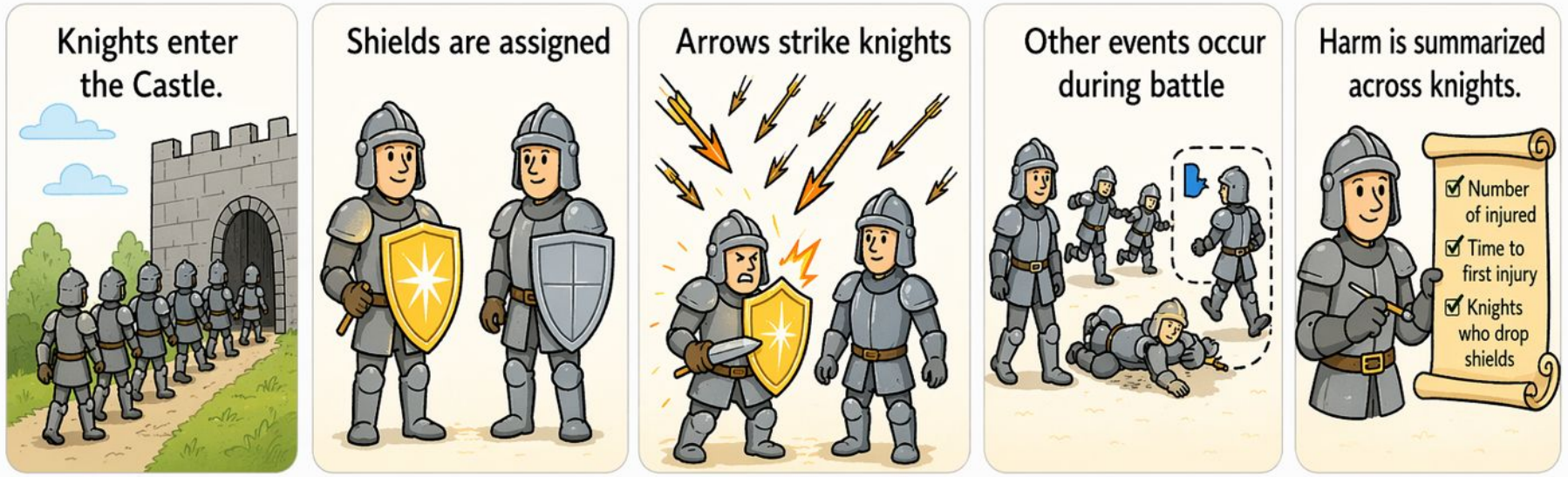
PHUSE Estimands in Safety Analytics Project



Building capability in safety analysis:

Producing educational materials and webinars **to operationalize the estimand framework for the safety analyses** in clinical trials

Knights using shields as protection from arrow wounds



Knights enter the Castle.

Shields are assigned

Arrows strike knights

Other events occur during battle

Harm is summarized across knights.

Population	Treatment	Safety endpoint	Intercurrent Events	Summary Measure
Knights	Gold vs Silver shields	Fatigue	• Shield dropped • Rescue armor added • Death	How fatigue is quantified across knights

Safety question:
What is the risk (%) of a safety event after starting to use gold shields compared to silver shields?

Estimand is the definition of how to respond to the question; described through the 5 attributes.

Learning Objectives

Define intercurrent events and identify common examples for safety analysis in clinical trials

Understand the difference between intercurrent events, competing risks and missing data

Describe common intercurrent events handling strategies for safety analysis in clinical trials

Compare and contrast various intercurrent event handling strategies

Handling Intercurrent Events

A. What is an intercurrent event?

B. Intercurrent event handling strategies

C. Learning checks and review

Intercurrent Events in a Clinical Trial



https://pixabay.com/photos/plot-pier-water-lake-house-villa-4231235/

An intercurrent event is something that happens to a person during a clinical trial that gets in the way of measuring what the researchers planned to measure.

An intercurrent event is like a plot twist that can mess with the results.

What is its formal definition,
what does it mean,
how to handle?

Intercurrent Event Definitions

1. ICH E9(R1) 2021: Events occurring **after treatment initiation** that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

2. Yuan et al 2021 (ASA SWG): Intercurrent events are the **post-randomization events** that potentially affect the existence and interpretation of the treatment effect and the inference on the treatment effect of the treatment of interest.

3. Mallinckrodt et al 2020: Intercurrent events are events that occur **after randomization** that alter the course of the randomized treatment.

ICH E9(R1) 2021 definition applies to both randomized and single arm studies. Whereas the other 2 definitions are interpretations of the ICH E9(R1) 2021 definition for a randomized study.

2) Yuan, Seifu et al. 2021. Estimands in safety and benefit-risk evaluation.
3) Mallinckrodt, Molenberghs et al. 2020. Identifying intercurrent events.

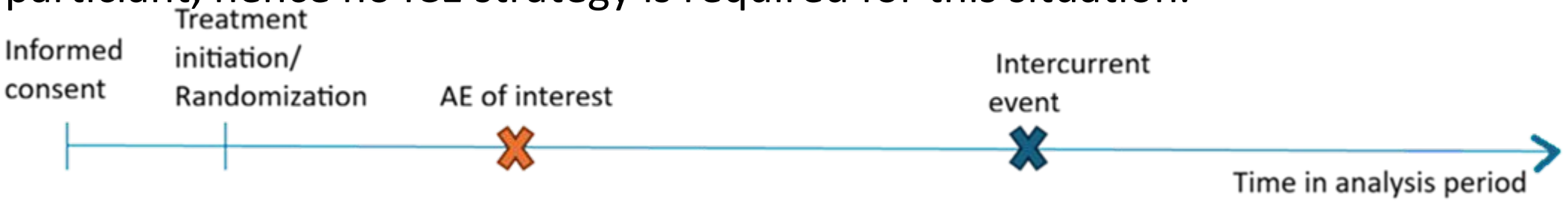
Order of occurrence of AE and ICE matters

A prespecified ICE is only considered an actual ICE for a given participant and AE of interest if, for that participant, the ICE occurs before the adverse event of interest.

- If ICE occurs before AE of interest for the participant: Apply proposed ICE strategy.

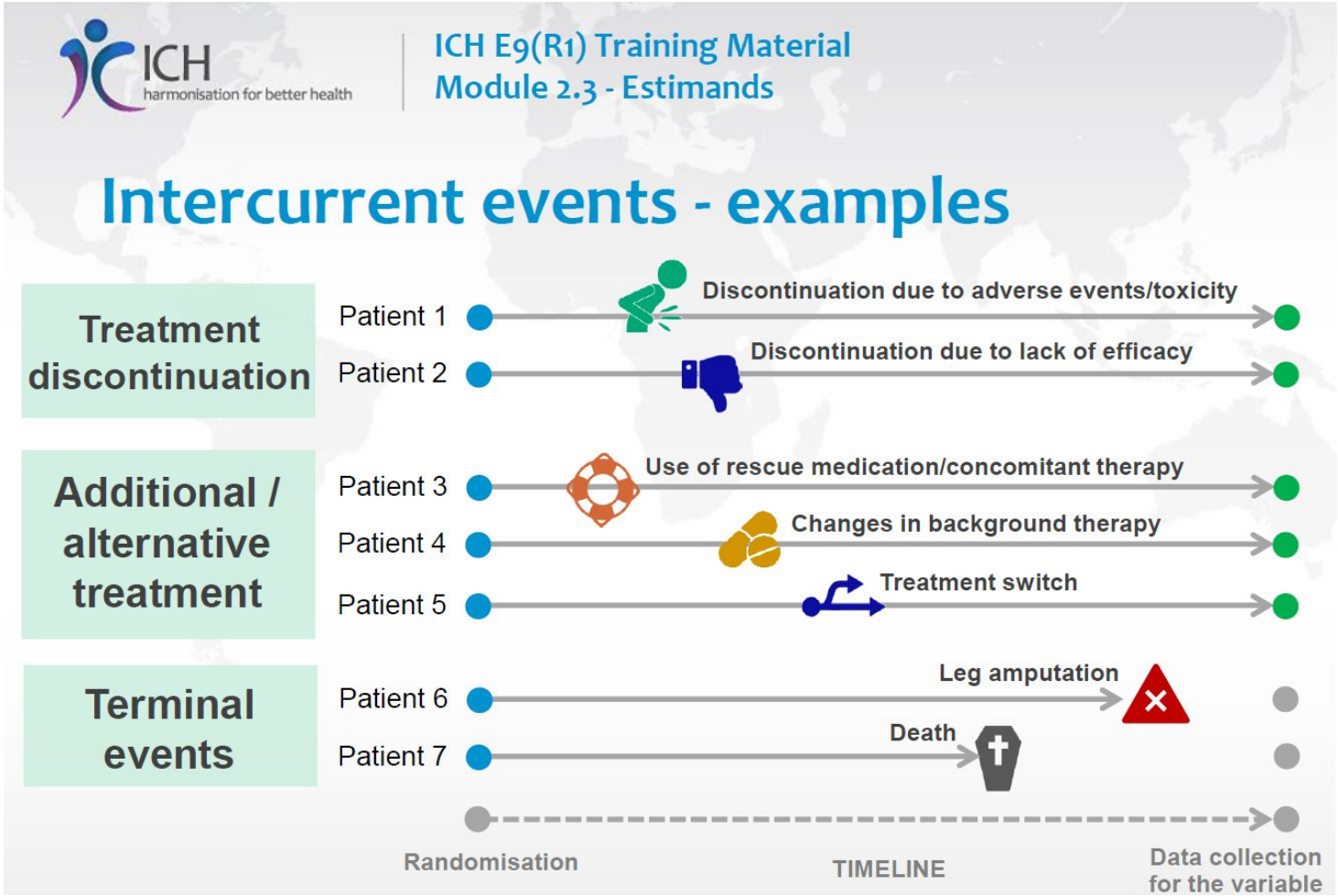


- If 'ICE' occurs after AE of interest for the subject: This is no ICE for this AE for this particiant, hence no ICE strategy is required for this situation.



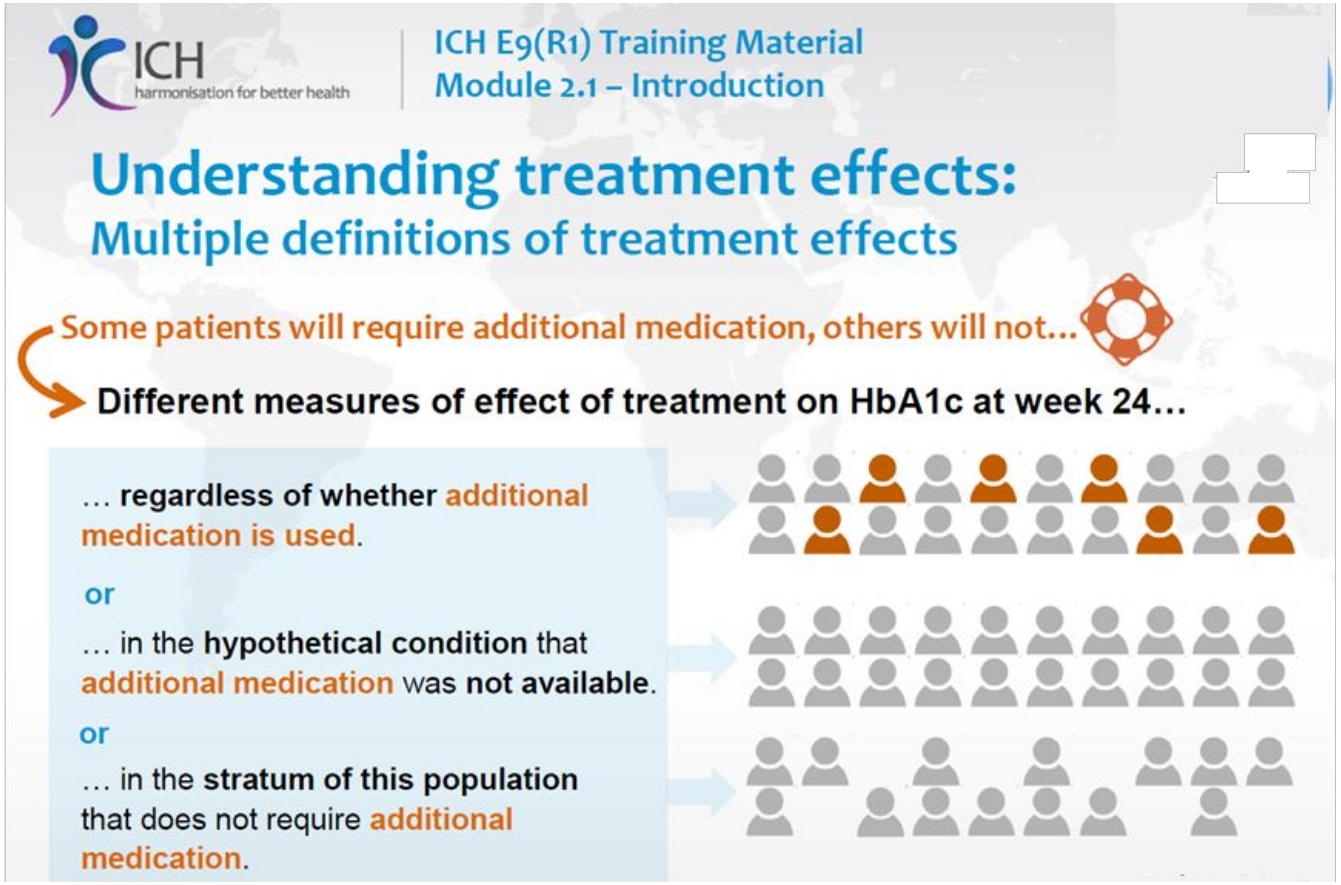
ICE intercurrent event

Typical Intercurrent Events



- Participants may experience a wide range of intercurrent events
- Safety analysis in a clinical trial typically implies addressing
  - treatment discontinuation
  - change in background medication including rescue medication
  - death

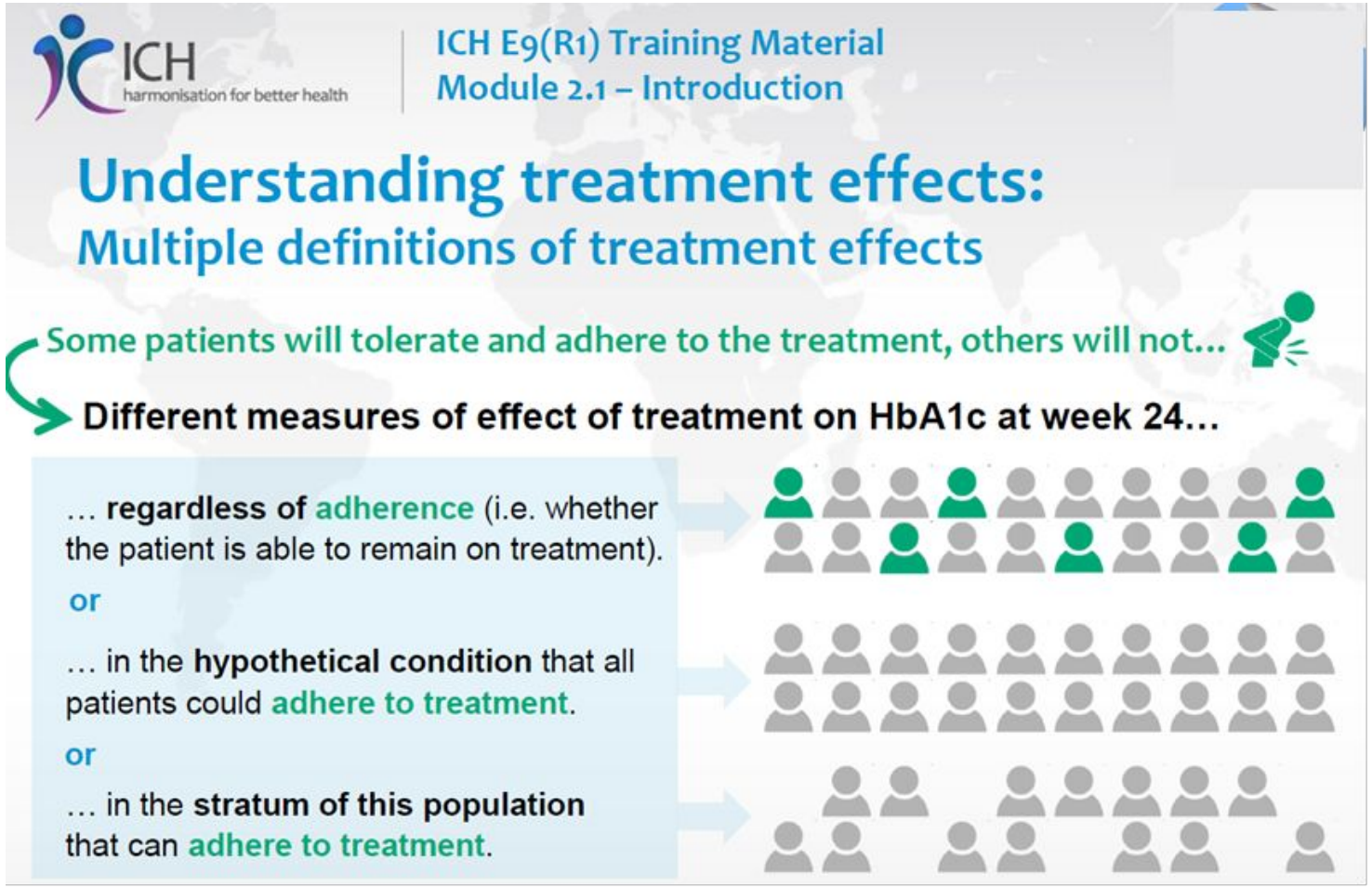
Understanding the treatment effect



- Intercurrent events are inherently connected to the definition of the treatment effect[1]
- The way we define the treatment effect in the clinical question defines the strategy for the intercurrent event

1) Mallinckrodt, Molenberghs et al 2020. Identifying intercurrent events.

Understanding the treatment effect, continued



Not all alternatives may be reliably estimated

- E.g., 'regardless of adherence' when subjects are terminating the study after premature treatment discontinuation

Not all alternatives may be equally acceptable for regulatory decision making

- E.g., stratum of subjects 'who adhered to the protocol' – the old per-protocol approach

Intercurrent event, Competing event, Missing data

What is the difference between intercurrent events, competing risks and missing data?



Contrasting Intercurrent Events and Competing Events

Intercurrent events are events occurring after treatment initiation (randomization) that affect either the interpretation or existence of the measurements associated with the clinical question of interest.[1]

An AE can always be subject to **competing risks**. The occurrence of the AE of interest might be precluded by the occurrence of the main time-to-event outcome, or another, fatal, AE.[2]

- All competing risks are intercurrent events
- In the typical interpretation, the competing event prevents data collection of interest for the clinical question, e.g.,
  - Safety events cannot be collected after participant died
  - Wound healing on a foot cannot be collected if the limb is amputated

1) ICH E9(R1) 2021; 2) Allignol et al 2016

Missing Data Does Not Constitute an ICE

Intercurrent events are NOT a missing data problem

- **Intercurrent events are meaningful** and provide information and are NOT to be thought of as a drawback to be avoided in clinical trials[1]

Missing data

- 'Missing data' are data that would be meaningful for the analysis of a given estimand but were not collected[1]
- **Administrative study withdrawal, loss-to-follow-up, and missing laboratory values due to instrument malfunction** are generally regarded as missing data, but not as intercurrent events[1]
- When planning a study, the team should consider strategies to prevent common causes of missing data.
- The **strategy to handle missing data should be aligned** to the clinical safety question and its estimand.

1) ICH E9(R1) Training material 2021

Handling Intercurrent Events

A. What is an intercurrent event?

B. Intercurrent event handling strategies

C. Learning checks and review

Typical Strategies for Intercurrent Events (ICEs)

TREATMENT POLICY The ICE is ignored in the analysis - however, the safety event of interest must be observable after the ICE

HYPOTHETICAL Participant's data is censored at the ICE - envisages a hypothetical scenario in which the ICE would not occur

WHILE-ON-TREATMENT or WHILE-ALIVE Used when response to treatment before the occurrence of the ICE is of interest

COMPOSITE Used when the ICE is considered to be informative about the participant's endpoint and is therefore incorporated into the definition of the endpoint

PRINCIPAL STRATUM Focusses on a subgroup defined by a potential occurrence (alternatively non-occurrence) of the ICE (e.g., participants who took a defined rescue medication)

ICH E9(R1) guidance and training; ICE intercurrent event

Cardiovascular Adverse Event Example

Four Possible Outcomes			
		Cardiovascular (CV) Event	
Rescue medica-tion for efficacy		No	Yes
	No	**A** No CV events were observed and rescue was not used	**B** CV event potentially caused by study treatment
	Yes	**C** No CV events were observed, but rescue was used	**D** CV event potentially caused by study treatment and/or rescue
	Total	A+C	B+D

For a participant, rescue medication is only regraded as an intercurrent event if initiated before the cardiovascular event happens

A, B, C and D are number of participants

Cardiovascular Adverse Event Example, continued

Choices	What to do if IE occurs	% CV Event	Strategy
Assume events are only relevant before ICE	Not using CV events after ICE in numerator	B / (A+B+C+D)	While-no-rescue
Ignore ICE	Use all CV events in the numerator	(B+D) / (A+B+C+D)	Treatment policy
Include ICE in the outcome	Add C to the B+D in the numerator	(B+C+D) / (A+B+C+D)	Composite
Assume ICE would not have occurred	Censor participant's data at timepoint of ICE	Estimate proportion with Kaplan-Meier approach	Hypothetical

Four Possible Outcomes			
		Cardiovascular (CV) Event	
Rescue medication for efficacy		No	Yes
	No	A No CV events were observed and rescue was not used	B CV event potentially caused by study treatment
	Yes	C No CV events were observed, but rescue was used	D CV event potentially caused by study treatment and/or rescue
	Total	A+C	B+D

For a participant, rescue medication is only regraded as an intercurrent event (ICE) if initiated before the cardiovascular event happens

A, B, C and D are number of participants

ICE Intercurrent event

Relation between the clinical question and the intercurrent event strategy for some typical clinical safety questions

Some of the following examples utilize statistical methodology beyond the scope of this presentation.

They are presented for the sake of completeness, but consultation with a ‘well seasoned’ statistician is encouraged.

The clinical questions are an extension to the definition in Polverejan E, O’Kelly M et al 2023

Format of Clinical Safety Question

What is the **percentage risk** of hypotension **within 3 months after initiation** of Treatment A *compared with placebo* in adults with hypertension?

Examples of typical adaptations

- Keep “percentage risk” and change the time window to “during the first 3 months of treatment”.
- Replace “percentage risk” with “incidence rate per 100 person-years” and change the time window to “during treatment”
- Omit “compared with [control]” in single-arm studies.

The format of the clinical question is an extension of the definition in Polverejan, O’Kelly et al (2023); and Hedman, Lisovskaja et al (2024)

Clinical Question & Intercurrent Event Strategy (1)

For treatment A compared with placebo in adults with hypertension

Intercurrent events: Treatment discontinuation, death

1. Traditional signal detection, evaluating risk

1a. What is the percentage risk of hypotension up to 3 months visit during treatment?

Not using participant's data after treatment discontinuation plus a grace period[1] and not imputing any data after death **(while-on-treatment and while-alive strategies)** and estimating probability of occurrence

1b. What is the percentage risk of hypotension up to 3 months visit after treatment initiation?

- Ignoring treatment discontinuation **(treatment policy strategy)**[2]
- Not imputing any data after death **(while-alive strategy)** and estimating probability of occurrence

1) Grace period is based on a function of drug's half-live; 2) Requiring data collection continues after the intercurrent event

Clinical Question & Intercurrent Event Strategy (2)

For treatment A compared with placebo in adults with hypertension

Intercurrent events: Treatment discontinuation, death

2. Signal detection evaluating risk at a specific timepoint



2a. What is the percentage risk of hypotension during the first 3 months of treatment?

Censoring participant's data after treatment discontinuation plus a grace period[1] and after death, by Kaplan-Meier approach **(hypothetical strategy)**

2b. What is the percentage risk of hypotension within 3 months after treatment initiation?

- Ignoring treatment discontinuation **(treatment policy strategy)**[2]
- Censoring participant's data after death by Kaplan-Meier approach **(hypothetical strategy)**

1) Grace period is based on a function of drug's half-live; 2) Requiring data collection continues after the intercurrent event

Clinical Question & Intercurrent Event Strategy (3)

For treatment A compared with placebo in adults with hypertension

Intercurrent events: Treatment discontinuation, death

3a. Signal detection evaluating incidence rate during treatment



What is the incidence rate of hypotension per 100 PY during treatment?

Not using participant's data after treatment discontinuation plus a grace period[1] and not imputing any data after death **(while-on-treatment and while-alive strategies)**, and estimating incidence rate per 100 PY

3b. Late latency AESI evaluating incidence rate after treatment initiation



What is the incidence rate of new-onset of diabetes per 100 PY after treatment initiation?

- Ignoring treatment discontinuation **(treatment policy strategy)**[2]
- Not imputing any data after death **(while-alive strategy)** and estimating incidence rate per 100 PY

1) Grace period is based on a function of drug's half-live; 2) Requiring data collection continues after the intercurrent event; PY person-years; AESI adverse event of special interest

Clinical Question & Intercurrent Event Strategy (4)

For treatment A compared with placebo in older adults with mild hypertension

Intercurrent events : Treatment discontinuation, death

4. Composite strategy



- If we expect that older adults who fall and sustain a hip fracture are at high risk of dying shortly afterwards; then, hip fracture and death can reasonably be combined into a composite endpoint.
- This approach can be used with any summary measure and can be combined with other strategies for other types of intercurrent events.

What is the percentage risk of hip-fracture or death within 1 year after treatment initiation?





1. Variable is a composite of hip-fracture and death **(composite strategy)**
2. Ignoring treatment discontinuation **(treatment policy strategy)**[1] and using Kaplan-Meier approach

1) Requiring data collection continues after the intercurrent event

Clinical Question & Intercurrent Event Strategy (5)

For treatment A compared with placebo in adults with hypertension

Key ICEs: Treatment discontinuation, death

Here we contrast the competing-risk and Kaplan–Meier approaches to handling death as an intercurrent event

5a. Treating death as competing event



What is the percentage risk of hypotension within 1 year after treatment initiation, while accounting for death as a competing event?

- Ignoring treatment discontinuation **(treatment policy strategy)**[1]
- Death is incorporated into the variable and analysis through a competing-risk model **(while-alive strategy)**

5b. Risk in a world where no one dies



Percentage risk of hypotension within 1 year after treatment initiation?

- Ignoring treatment discontinuation **(treatment policy strategy)**[1]
- Censoring participant's data after death by Kaplan-Meier approach **(hypothetical strategy)**

1) Requiring data collection continues after the ICE(s)

Clinical Question & Intercurrent Event Strategy (6)

For treatment A compared with placebo in adults with hypertension

Intercurrent events: Treatment discontinuation, death, a specific rescue medication

What if a specific rescue intervention should not be ignored?
We first evaluate the safety profile without confounding by this rescue intervention.

6a. Rescue is not available

What is the percentage risk of hypotension within 1 year after treatment initiation, assuming that rescue is not available?

- Censoring participant's data at 1st administration of the defined rescue medication and after death by using Kaplan-Meier approach **(hypothetical strategy)**
- Ignoring treatment discontinuation **(treatment policy strategy)**[1]

6b. While no rescue

What is the incidence rate of hypotension per 100 PY during treatment while no rescue?

- Not using participant's data after 1st administration of the defined rescue intervention and not imputing any data after death **(while-no-rescue and while-alive strategies)** and estimating incidence rate per 100 PY
- Ignoring treatment discontinuation **(treatment policy strategy)**[1]

1) Requiring data collection continues after the ICE(s); PY Person-years

Clinical Question & Intercurrent Event Strategy (7)

For treatment A compared with placebo in adults with hypertension

Intercurrent events: Treatment discontinuation, death, a specific rescue medication

Will the safety profile be markedly worse in those who were exposed to a combination of treatment and this rescue?

7. Principal stratum strategy

After study treatment initiation, what is the percentage risk of hypotension within 1 month after initiation of rescue medication among participants in the stratum who received the defined rescue medication?

1. After study treatment initiation, select the participants who got the defined rescue intervention **(principal stratum strategy)**
2. Ignore treatment discontinuation **(treatment policy strategy)**[1], and censor data after death by Kaplan-Meier approach **(hypothetical strategy)**

- WARNING - The initial randomization is NOT handling this analysis, so any treatment group comparisons rely on proxy randomization created via causality modelling (for example, propensity score modelling)

1) Requiring data collection continues after the ICE(s)

Intercurrent Event Handling Summary

- For **each clinical question, define an estimand** comprising a definition of the population, a single endpoint, a single summary measure, and a set of intercurrent events of importance to the clinical question.[1]
- For **each intercurrent event** of importance to a clinical question, **define a handling strategy** that is aligned with the clinical question.
- Different intercurrent events may require different handling strategies
- Note that the strategy for handling missing data should also be aligned with the clinical question and its estimand.



AI-generated

1) Polverejan, O'Kelly et al 2023

Handling Intercurrent Events

A. What is an intercurrent event?

B. Intercurrent event handling strategies

B. Learning checks and review

Learning Check #1

Which of the following is NOT typically considered an intercurrent event?

A. Premature treatment discontinuation

B. Use of rescue medication

C. Administrative study withdrawal

D. Too so sick for continuing the study

Learning Check #1

Which of the following is NOT typically considered an intercurrent event?

A. Premature treatment discontinuation

B. Use of rescue medication

C. Administrative study withdrawal

D. Too so sick for continuing the study

Learning Check #2



Match the statement on left with the option on the right:

A) Participant prematurely terminates randomized treatment

B) Participant was withdrawn from the study because of too high disease progression

C) Participant made administrative study withdrawal

D) Participant died during the study

E) Hematology laboratory parameters were missing because subject too sick to make the study visit

F) Hematology laboratory parameters were missing due to instrument malfunction

1) Intercurrent event

2) Missing data issue

Learning Check #2



Match the statement on left with the option on the right:

A) Participant prematurely terminates randomized treatment

B) Participant was withdrawn from the study because of too high disease progression

C) Participant made administrative study withdrawal

D) Participant died during the study

E) Hematology laboratory parameters were missing because subject too sick to make the study visit

F) Hematology laboratory parameters were missing due to instrument malfunction

1) Intercurrent event

2) Missing data issue

Learning Check #3



Are the following statements true or false?

A) An estimand is typically comprised of (among other attributes) a single endpoint and a single intercurrent event (with multiple handling strategies) to answer a single research question.

__ True __ False

B) An estimand is typically comprised of (among other attributes) a single endpoint and a handful of intercurrent events (which each has a handling strategy) to answer a single research question.

__ True __ False

Learning Check #3



Are the following statements true or false?

A) An estimand is typically comprised of (among other attributes) a single endpoint and a single intercurrent event (with multiple handling strategies) to answer a single research question.

__ True _X_ False

B) An estimand is typically comprised of (among other attributes) a single endpoint and a handful of intercurrent events (which each has a handling strategy) to answer a single research question.

_X_ True __ False

Learning Objectives – Review

Define intercurrent events (ICEs) and identify common examples for safety analysis in clinical trials

ICEs are events occurring after treatment initiation (or randomization; as per definition in the study) that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

ICEs that typically require a handling strategy in the safety analysis of a clinical trial are

- treatment discontinuation
- change in background medication including rescue medication
- death

Learning Objectives – Review

Describe common intercurrent events handling strategies for safety analysis in clinical trials

The clinical question drives the selection of the strategy for the specific intercurrent event (ICE) and this is realized by the handling of the subject's data after the ICE in the analysis.

- Treatment policy Ignore ICE
- Hypothetical Censor participant's data after treatment discontinuation plus a grace period[1]
- While-on-treatment Not using participant's data after treatment discontinuation plus a grace period[1]
- Composite Incorporate ICE into definition of the endpoint
- Principal strata Incorporate ICE into definition of the analysis population

1) Grace period is based on a function of drug's half-live

Learning Objectives – Review

Compare and contrast various intercurrent event handling strategies

Re-visit the examples in this presentation



https://pixabay.com/photos/blonde-girl-bridge-fun-happy-joy-1868815/

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