



On the role of hypothetical estimand strategies in clinical trials

Caught between a rock and a hard place

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Disclaimer

The slides reflect our current thinking rather than offering specific solutions or advice at this point. They are meant to facilitate discussions and exchange of experience.

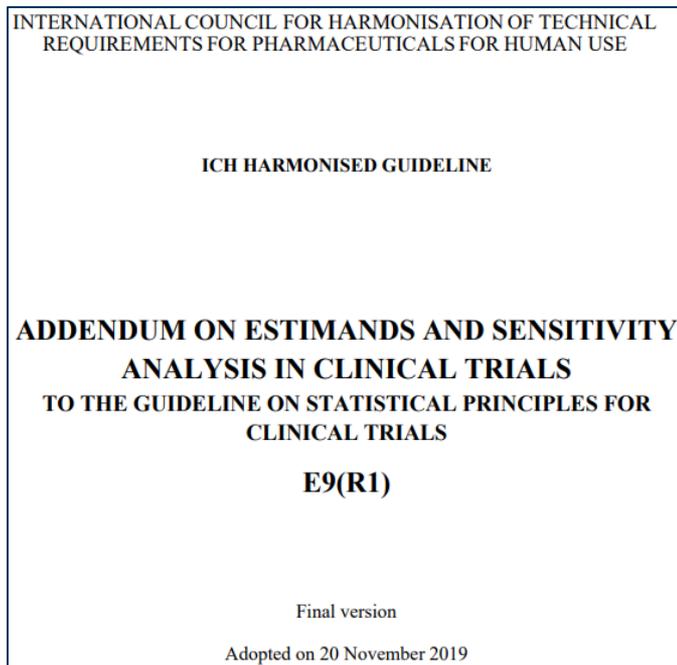
Outline

- Brief reminder about the 'estimand framework' (ICH E9 addendum)
- Hypothetical strategies and the need for precise definitions
- Examples of hypothetical scenarios
- Conclusions

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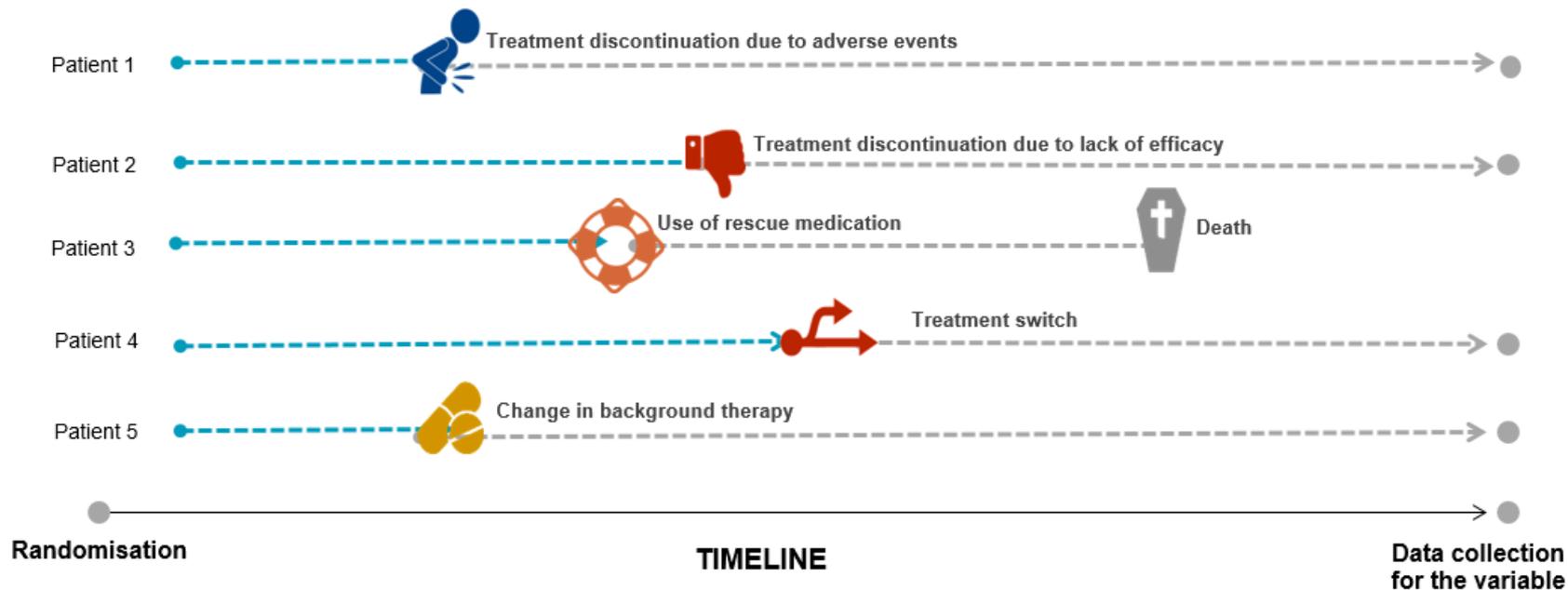
ICH E9(R1)



Estimand

A precise description of the treatment effect reflecting the clinical question posed by the trial objective.

Patient journeys and intercurrent events



An **intercurrent event** is an event that occurs after randomization/treatment initiation and either **precludes observation** of the variable or **affects its interpretation**.

Strategies to address intercurrent events

ICH E9(R1) discusses five strategies to address intercurrent events

Example: 'Intake of additional medication'

Treatment policy: Treatment effect regardless of the intercurrent event

e.g. 'Drug, plus additional medication as needed' vs. 'Placebo, plus additional medication as needed'

Hypothetical: Treatment effect if the intercurrent event did not occur

e.g. 'Effect of Drug vs Placebo if additional medication had not been taken'

Composite: Occurrence of intercurrent event included in the endpoint definition

e.g. 'Intake of additional medication is considered a treatment failure'

Principal Stratum

While on Treatment

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Hypothetical strategies – ‘What if...’

According to ICH E9(R1):

*“A **scenario is envisaged in which the intercurrent event would not occur: 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.**”*

*A wide variety of hypothetical scenarios can be envisaged, but **some scenarios are likely to be of more clinical or regulatory interest than others.**”*

Broad range hypothetical scenarios can be considered

The hypothetical scenario 'if additional medication had not been taken' is not precise enough

- What would the treatment effect be, **had additional medication not been made available?**
 - May be plausible to ask this question if additional medication was optional
 - Presumably patients would have more severe symptoms if additional medication was withheld
- What would the treatment effect be, **had patients not needed additional medication and *behaved like other patients who did not take additional medication?***
 - Not clear what plausible scenario would lead to 'patients not needing additional medication'
 - Not clear why patients who needed additional medication would behave like patients not needing additional medication
- What would the treatment effect be, **had patients not needed additional medication and *behaved like placebo patients?***
 - Not clear what plausible scenario would lead to 'patients not needing additional medication'
 - Not clear why patients who needed additional medication would behave like placebo patients thereafter

Broad range hypothetical scenarios can be considered

The hypothetical scenario 'if additional medication had not been taken?' is not precise enough

- Importantly, speaking of 'THE hypothetical' leaves too much room for ambiguity → a precise language is required to explain how the hypothetical scenario is realized

- Numerous hypothetical estimands can be formulated – some are more useful and clinically plausible than others

- Not clear why patients who needed additional medication would behave like placebo patients thereafter

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How to ensure the relevance of a hypothetical scenario?

In the following, we use several examples to delineate different hypothetical scenarios, from less to more clinically relevant

1. Severe pain indication
2. Nasal polyp indication
3. Rare and progressive renal indication, no approved therapies
4. Treatment switching in a placebo-controlled trial
5. Kidney transplantation in dialysis patients

Disclaimer: Examples have been simplified for the purpose of this presentation

1. Severe pain indication

Phase III trial investigating a new drug in patients with severe pain

- Short-term use of rescue medication (the intercurrent event) is allowed for ethical reasons, otherwise patients may commit suicide during intense pain attacks

What is the (scientific / clinical / regulatory) relevance of the following two hypothetical scenarios?

- A. Treatment effect is of interest had patients not needed rescue medication
→ Is it realistic to assume that the patients' behavior can be changed accordingly?
- B. Treatment effect is of interest had rescue medication not been made available to patients
→ Would it be conceivable to run such a trial in practice?

Both hypothetical scenarios are different, but neither of them is of clinical relevance in this particular setting

1. Severe pain indication

Phase III trial investigating a new drug in patients with severe pain

Importantly, short-term use of rescue medication is not optional: It will be a key part of a future treatment strategy in conjunction with the new drug and withholding it from patients is unreasonable.

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But what are the implications for the approval and labelling process? Will it be for 'drug', or for 'drug, plus rescue medication as needed'? If the latter, will it be for a specific rescue medication and what happens if after some time it is no longer part of clinical practice?

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Both hypothetical scenarios are very different, but neither of them is of clinical relevance in this particular setting

2. Nasal polyp indication

Surgery is an intercurrent event and the question is **whether a hypothetical estimand ('if surgery had not been made available') is clinically meaningful**

While surgery is **common clinical practice**, arguing that a hypothetical estimand is therefore neither of clinical nor of regulatory interest leaves room for ambiguity

What if the decision to perform surgery is optional, for example:

- at the discretion of the investigator?
- due to regional differences?
- comorbidities limit some patients to have the surgery?

2. Nasal polyp indication

Surgery is an intercurrent event and the question is whether a hypothetical

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Need for surgery may indicate that the drug is ineffective, in which case it should be part of the outcome definition

Use of a composite strategy seems reasonable (e.g., by assigning surgery the worst outcome on an existing ordinal scale)

Importantly, a composite strategy is reasonable for clinical reasons, not because a hypothetical strategy is unreasonable

3. Rare and progressive renal indication, no approved therapies

Rare renal disease leading to ~50% patients progressing to kidney failure

Primary endpoint of proteinuria assessed in a placebo-controlled trial

Due to lack of approved treatments and despite increased infection risk, patients are often treated with immunosuppressants to reduce proteinuria with the hope to improve kidney function

- In a placebo-controlled setting, immunosuppressants may be prescribed as rescue during the trial
- However, such therapies are not desired as part of a future treatment strategy, if the new treatment is shown to be beneficial

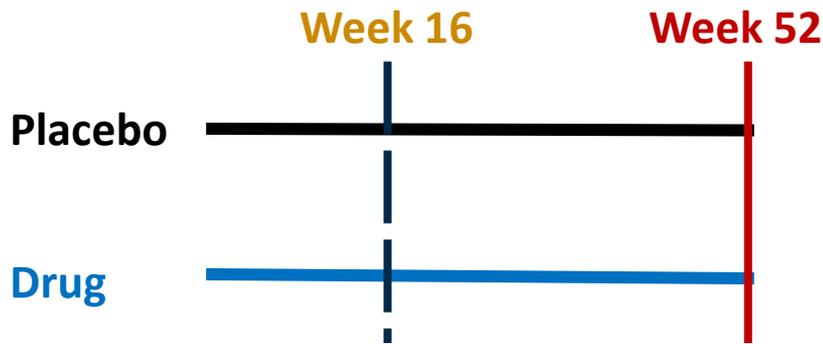
Conclusion: It seems reasonable to evaluate the treatment effect in a hypothetical scenario where immunosuppressants were not made available

4. Treatment switching in a placebo-controlled trial

Randomized, double-blind, placebo-controlled Phase III study

Compare a new drug versus placebo in the treatment of an inflammatory disease

Clinical measurement of interest: continuous symptom score at week 52



- Patients are allowed to switch to rescue therapy (essentially new drug itself) after week 16 if symptoms are not controlled
- No deterministic rule for switching to rescue
- Many placebo patients are expected to switch to new drug after week 16

4. Treatment switching in a placebo-controlled trial

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What is the role of hypothetical estimands in placebo-controlled trials?

- The fact that we are conducting a placebo-controlled trial suggests that we want to tease out the 'pure treatment effect' of drug versus placebo
- If administration of placebo is questionable for ethical reasons, patients have to be offered the possibility to switch to an alternative treatment option or use rescue

In such settings, it is conceivable that a hypothetical estimand is of regulatory interest

If a 'pure treatment effect' is not of interest, then the design seems to be inappropriate
→ if real clinical practice was of interest, wouldn't we consider running more pragmatic trials and limit the use of placebo-controlled trials?

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5. Kidney transplant in dialysis patients

Chronic kidney disease where patients need dialysis

Consider a two-year study to either compare two types of dialysis on morbidity and mortality or investigate the effect of a drug intended to reduce the frequency or number of dialysis sessions

A minority of patients will be eligible for a renal transplantation during this period

- this is neither due to treatment toxicity nor a trial endpoint
- it would not be possible to anticipate in advance who will get a transplant and when a donor kidney will be available

Hence a transplant can be considered a randomly occurring intercurrent event and the patient would be withdrawn from the study

It could well be of interest to ask the question of what would have been the outcome of interest in the arms had the patients not been withdrawn for transplant

Summary of examples

Intercurrent event (IE)...	Example	Strategy
... is part of a future treatment strategy	Short term pain medication in severe pain indication	Treatment policy: The IE is part of the treatment strategy
... is outcome-related (possibly even being an efficacy endpoint in its own right)	Surgery in nasal polyp indication	Composite strategy: Assign worst outcome on an existing ordinal scale
... is a medication or procedure which is necessary to offer for ethical reasons, but is not desired as part of a future treatment strategy	Off-label rescue medication in rare renal disease Treatment switch if symptoms are not controlled	Hypothetical strategy: A scenario is envisaged to assess the pure treatment effect of the new drug
... prevents the outcome being observed, but is expected to occur randomly and is not thought to be impacted by the treatment	Kidney transplant in dialysis patients	Hypothetical strategy: A scenario is envisaged in which the IE would not occur

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Relevance of hypothetical scenarios

- ICH E9(R1) acknowledges that “*some scenarios are likely to be of more clinical or regulatory interest than others*”
- While it does not provide guidance on assessing the relevance of hypothetical scenarios, it suggests a **two-step approach**:
 - **Hypothetical scenarios that cannot possibly occur in clinical practice** are likely irrelevant and **should be avoided** for a primary estimand in a confirmatory trial
 - For example, it may not be reasonable to hypothesize a scenario where patients fully adhere to their treatment notwithstanding serious adverse events
 - **Otherwise**, a hypothetical strategy might be of interest, but...
 - **clinical plausibility** remains to be justified in each case
 - **statistically valid and robust analysis** approaches must be ensured

Conclusions

We argue that

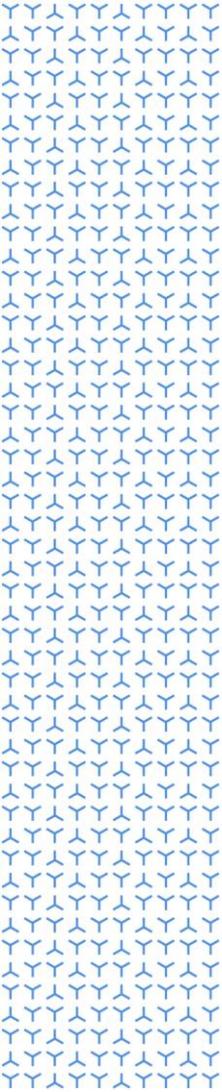
- the class of **hypothetical estimands is very broad** and a precise definition is crucial to enable a fruitful discussion with different stakeholders
- the hypothetical scenario being envisaged must be **plausible in real life** ('positivity' assumption)
- arguments in favor of/against hypothetical estimands are often subtle and a **thorough justification is needed** when engaging with different stakeholders
- it is a **joint discussion between clinical and statistics**

Recommendations

- **Early discussions with the agencies** regarding the most appropriate estimand for the situation at hand
- Ensure that an **analysis approach is in place that aligns with the estimand** (i.e., the hypothetical scenario being envisaged)
 - Importantly, **this includes sensitivity analyses** to evaluate the robustness of the conclusions

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