An Appraisal of the ICH E9(R1) Intercurrent Event Definition with Case Examples

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***Please send feedback regarding our proposed definition to senglert@its.jnj.com**

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Background

The ICH E9(R1) addendum on estimands and sensitivity analysis in clinical trials introduces the term *Intercurrent Events* as a core concept; so important that it uses this term 106 times. Discussions within the EIWG revealed inconsistencies in the understanding and interpretation of the definition of intercurrent events. The EIWG has formed a sub-team on intercurrent events (ICEs) to identify areas of uncertainty in ICH E9(R1) and to provide recommendations for its implementation.

Objective

This poster is on the question if certain events meet the glossary definition of an ICE. Having a solid understanding of what ICEs are is essential for setting clear clinical trial objectives.

Methods

Through a series of case examples, we highlight some of the shortcomings of the current definition as well as areas of different interpretation.

Conclusion

We believe that the addition “after treatment initiation” can be restrictive and should be understood as “after treatment assignment”. Some intercurrent events may occur prior to treatment assignment (and initiation) but be identified subsequently. It is sometimes helpful to also identify these as intercurrent events and suggest adding that option.

We believe that the term “existence of the measurements” needs clarity and further explanation.

We use the term "outcomes" in our alternative definition to emphasize that the biological property that is measured is relevant in the definition, not the measurement itself. Events that lead to missing data or estimation challenges should be discussed within the analysis considerations not the estimand.

Recommendation

Our proposed definition for ‘intercurrent event’:

Events identified or occurring after treatment assignment that affect the interpretation of the outcome associated with the clinical question of interest, or terminal events, such as death or amputation, beyond which the outcome does not exist.

Reference

ICH E9 (R1), Step 5, European Medicine Agency EMA/CHMP/ICH/436221/2017 (2020)

Intercurrent Events, ICH-E9(R1), Glossary Definition

“Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.”

Case Example 1: events occurring between treatment assignment and treatment initiation

- An open-label trial compares a new drug vs. standard-of-care
- The clinical question of interest targets a treatment-policy approach
- Patients withdraw early and don’t receive any study medication
- ‘Treatment not initiated’ should be an intercurrent event to describe how these events relate to the clinical question of interest

Case Example 2: positive result in baseline sample is reported by laboratory test after treatment initiation

- A prophylactic vaccine trial compares a new vaccine with placebo
- The clinical question of interest is on vaccine efficacy in a population free from the target infection at the time of vaccination
- ‘Infections that occur prior to/at baseline’ but manifest and get detected after treatment initiation should be intercurrent events

Case Example 3: the sample used to determine the outcome is not sufficient

- In a tuberculosis trial, the outcome reflecting the clinical question of interest was defined as the presence of TB in a sputum sample
- At their final visit, some patients cannot produce any/enough sputum to perform a test.
- Is the lack of sputum an intercurrent event that defines the clinical question of interest, or does it result in missing data and needs to be addressed in analysis?

Case Example 4: non-compliance with the timing of outcome assessments

- A vaccines trial where the clinical question is on immune response
- Timing of the sampling post-vaccination may profoundly impact the immune response measure. As such, it may impact the immunogenicity comparison between treatment groups and may jeopardize the ability to properly quantify the immune response
- Is “non-compliance with blood sampling window” a quality issue with study conduct and/or an intercurrent event?

Case Example 5: clinical events impacting outcome and its ability to be measured

- In a septic shock study, the clinical question is for neurological function which can only be measured in a conscious state
- Some patients are put into a reversible induced coma, suppressing the networks used to generate consciousness and allowing the brain to rest.
- Is induced coma a terminal event and/or should it be considered as an ICE? It affects the outcome and ability to be measured.

The working group thinks further guidance is needed to help address the uncertainty around these cases and we value your input.

Summary	Doesn’t take treatment	Post treatment identification	Sampling deviation	Failure to measure	Terminal events
Glossary definition	✗	✗	?	?	✓
Proposed definition	✓	✓	✗	✗	✓