ICH E9(R1) Addendum – Blessing or curse?

Date

Norwegian Medicines Agency
ICH E9(R1), Purpose and Scope

- However, the question remains whether estimating an effect in accordance with the ITT principle always represents with the treatment effect of greatest relevance to regulatory and clinical decision making.

- The framework outlined in this addendum gives a basis for discussing other treatment effects and some points to consider for the design and analysis of trials to give estimates of these treatment effects that are reliable for decision making.
Explain the why and what

• With precise specification of an agreed estimand and a statistical analysis that is both aligned to the estimand and pre-specified to a level of detail that it can be replicated precisely by a third party, regulatory interest can focus on sensitivity to deviations from assumptions and limitations in the data in respect of a particular analysis.

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• 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. Missing data must be defined and considered in respect of a particular estimand.
Supplementary Analyses

• Supplementary analyses (see Glossary) generally play a secondary role for interpretation of trial results, though can provide additional insights.

• However, those investigations might be considered as the main analysis of another estimand of interest. *

• Glossary: Is a general description for analyses that are conducted in addition to the main and sensitivity analysis with the intent to provide additional insights into the understanding of the treatment effect.
This should sound familiar......

• The protocol and the analysis plan should **pre-specify the main estimator that is aligned with the primary estimand and leads to the primary analysis**, together with a **suitable sensitivity** analysis to **explore the robustness** under deviations from its assumptions.

• Estimands for **secondary trial objectives** (e.g. related to secondary variables) that are likely to support regulatory decisions should also be defined and specified explicitly, each with a corresponding main estimator and, if appropriate, a suitable sensitivity analysis.

• Additional exploratory trial objectives may be considered for exploratory purposes, leading to additional estimands.
So what is your verdict, a blessing or a curse?
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