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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Sensitivity analyses

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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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