Implications of the ICH E9 estimand addendum on how we develop, run, and analyse clinical trials

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What is the ICH E9 addendum?

ICH E9 draft addendum

ICH E9: “Statistical principles for Clinical Trials.”

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1998.

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Why amend E9?

ICH E9 draft addendum

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Why amend E9? **Lack of alignment** between trial objectives and reported effect quantification.

What is a “treatment effect”?

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Counterfactual! Average treatment effect.

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- **not** received treatment,
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Counterfactual! Average treatment effect.

Estimate from **randomized clinical trial**.

Example: Autism spectrum disorder

Ambiguity!

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Treatment difference between Balovaptan and placebo on the Vineland Score at Week 24.

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Some patients will tolerate Balovaptan and **adhere** to its administration schedule, others will not.

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Objective:

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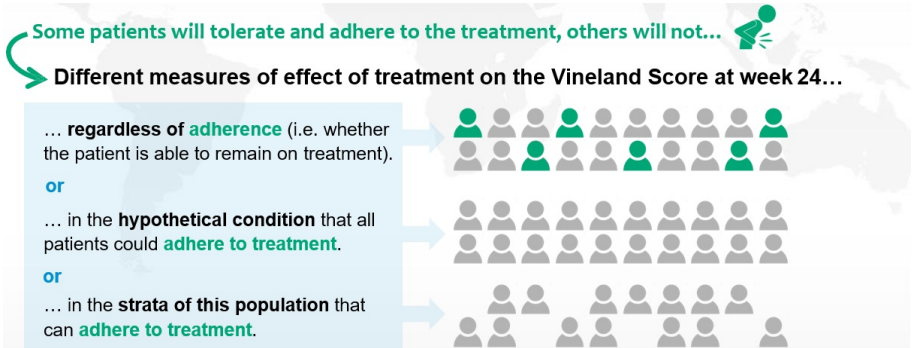
Ambiguity!

Some patients will **require changes in dose or administration** of additional medication (e.g. concomitant or rescue medication, treatment switch, etc.), others will not.

Multiple definitions of treatment effect



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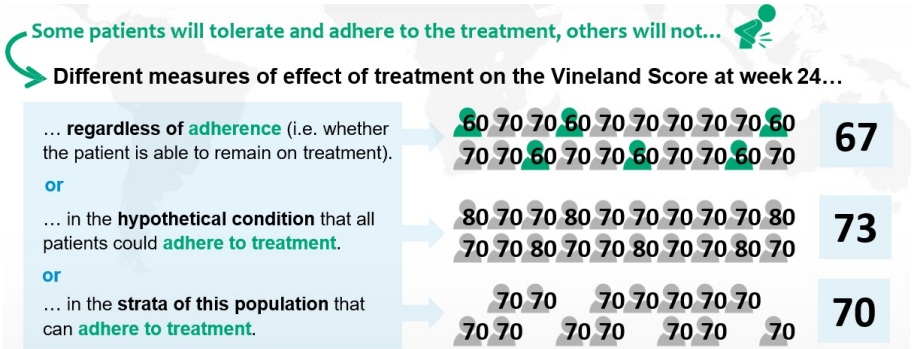

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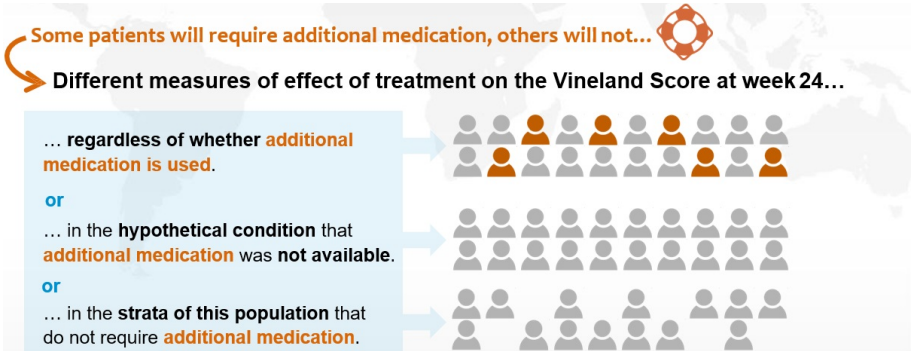

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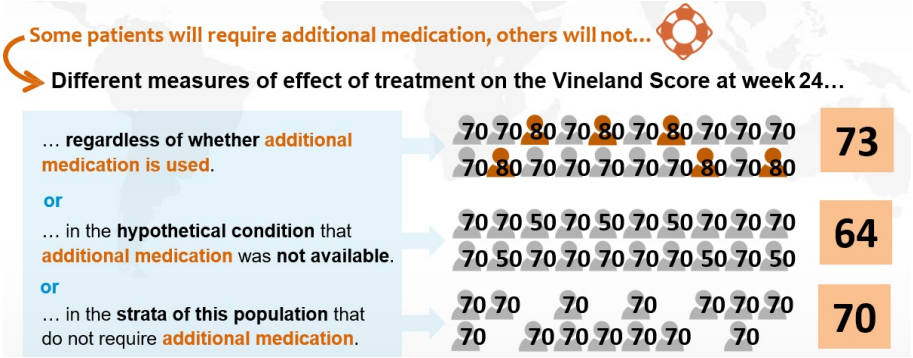

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Understanding treatment effects

- Multiple definitions of **treatment effect**.
- Different definitions addressing **different scientific questions**.
- Not all equally acceptable for **regulatory decision making**.
- Regulatory vs. HTA / payer decision making.
- Not all alternatives can be reliably estimated!

How does the addendum intend to fix this?

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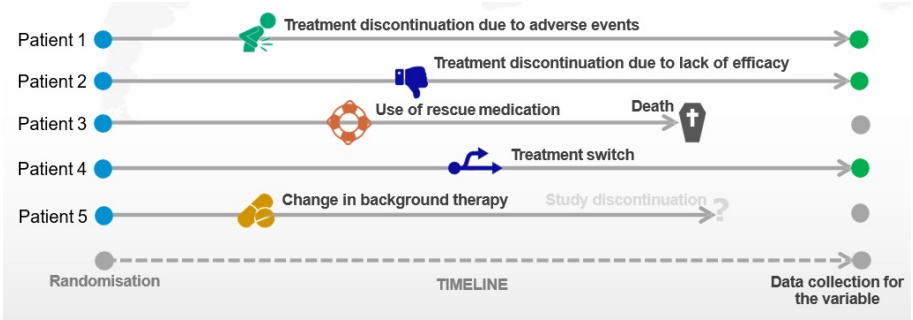
More precise definition of trial objective $\Rightarrow$ estimand!

Intercurrent events

Events that occur after treatment initiation and either **preclude observation of the variable or affect its interpretation**.



Estimand attributes

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- Population.
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- Population-level summary of variable.

Objective pre- and post-addendum

Treatment difference between Balovaptan and placebo on the Vineland Score at Week 24.

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The trial will compare 10mg Balovaptan tablets administered at weeks 4, 8, 12, 16, 20 with matching placebo in Autism spectrum disorder patients. The primary comparison of interest is the mean difference in change from baseline of the Vineland score at 24 weeks. The primary trial objective is to demonstrate superiority of the experimental over the control treatment. The primary comparison will be made regardless of whether patients withdraw due to study-drug related reasons and assuming no non-study-drug related withdrawals were possible.

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Estimand follows from precise trial objective.

Impact

Impact on data collection

- Estimand **dictates data that need to be collected**.
- Each trial likely to have **multiple estimands** $\Rightarrow$ different estimands might require different data!
- Requires **multi-disciplinary** involvement from **earliest stages** of clinical trial development.
- Impacts **design of eCRF** or other data collection tools and monitoring strategy.
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Might need to reflect this in **sample size computation**!

Broader impact

Aligning drug developers and regulatory bodies' expectations for target treatment effect **upfront** has potential to give:

- More **meaningful** descriptions of treatment effects for licensing and prescribing decisions.
- Clinical trials with designs that are **aligned to agreed objectives**.
- Increased **transparency** with respect to data analysis and inference.
- More **predictable** regulatory assessment procedures.
- More **flexibility** from regulators.
- **Reduction in total number of analyses** (primary + secondary + sensitivity).
- Clear language to describe and discuss different estimands required by different stakeholders.
- **Shift of resources** from analysis / filing to design.

Are we pushing boundaries?

We push boundaries!

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Post-addendum: EMA Q&A document that opens door to such analyses **IF**:

- strong arguments to justify it,
- **preplan** everything,
- ensure **quality** throughout protocol, proper data collection, and analysis.

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Secondary progressive multiple sclerosis:

- Primary objective: efficacy of siponimod relative to placebo in delaying disability progression.
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Derivation and estimation: Magnusson et al. (2019).

Thank you for your attention.

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References I

- Magnusson, B. P., Schmidli, H., Rouyrre, N. and Scharfstein, D. O. (2019). Bayesian inference for a principal stratum estimand to assess the treatment effect in a subgroup characterized by postrandomization event occurrence. *Statistics in Medicine* **0**.
  https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.8333

Backup slides

Six strategies for addressing intercurrent events

Three strategies define estimand attributes:

- Composite strategy $\Rightarrow$ impacting variable definition.
- Principal stratum strategy $\Rightarrow$ impacting population definition.
- Treatment strategy $\Rightarrow$ impacting treatment definition.

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Three strategies addressing remaining intercurrent events:

- Treatment policy strategy $\Rightarrow$ disregard ICEs.
- Hypothetical strategy $\Rightarrow$ assume ICE had not happened.
- While on treatment strategy $\Rightarrow$ consider until ICE.

General implications of the addendum

Framework and language

- Promote alignment between trial objectives, design, data collection, conduct, analysis and inference.
- Promote understanding that trial objectives cannot be translated into estimands without reflecting how potential intercurrent events are addressed in scientific question of interest.
- Promote discussion of different strategies to handle intercurrent events to identify and describe treatment effects that reflect scientific questions of interest.
- Define treatment effect of interest - before a trial is designed and conducted - that is relevant in clinical practice.
- Highlight importance of considering whether main analysis provides estimate which is reliable for inference.
- Re-define missing data.
- Re-define sensitivity analysis and regulatory assessment of robustness.
- Introduce supplementary analysis as any other analysis to fully investigate and understand trial data.

Impact on documentation

Protocols	Study population	Derive population from estimand definition
	Study intervention	Derive intervention from estimand definition, including rescue medicine
	Discontinuation	Derive discontinuation actions from intercurrent event strategies in estimand definition
	Statistical considerations	Hypothesis, analysis sets, sample size, endpoints follow from estimand definition Separate sensitivity from supplementary analyses.
Additonally for SAPs	Sample Size	Optionally provide (even) more details how intercurrent events are taken into account in sample size computation
Additonally for CSRs	Discontinuation	Tabulate observed intercurrent events.
	Changes in Planned Analyses Prior to Unblinding or DB lock	Discuss how intercurrent events that were not foreseen at the design stage, or identified during the conduct of the trial, were handled. Discuss not only the choices made for the analysis, but the effect on the estimand.

Doing now what patients need next

R version and packages used to generate these slides:
R version: R version 3.6.0 (2019-04-26)
Base packages: stats / graphics / grDevices / utils / datasets / methods / base
Other packages:

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