ICH E20 guideline on adaptive designs for clinical trials: My reflections as a statistician working in industry

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Disclaimer

This presentation was prepared during my employment at Johnson & Johnson

It represents my personal view and is no way representative of any official JnJ position

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Featured Article

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Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls

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THIS PAPER WAS PUBLISHED 10 YEARS AGO

WE SEEM TO BE FOCUSSING ON THE PITFALLS, NOT THE OPPORTUNITIES

The Ghost Is Not That Scary

PITFALLS ARE HIGHLIGHTED

Heavy emphasis on type I error rate control

Increased requirements for justification as compared to fixed designs which are not always warranted

SOME OPPORTUNITIES ARE NOT MENTIONED

Increased speed in decision making

- Futility
- Early efficacy

Use in special situations

- Rare diseases

Key Principles Section

Key principles not unique to adaptive trials

Especially applies to „Adequacy within the development program“

Clinical trials need to answer certain questions at certain stages of the development program

→ If they do not, then the development program is inadequate

→ It‘s not necessarily the adaptive features that render a design inadequate

Similar comments apply to „Adequacy of trial planning“

Undue Pressure on Adaptive Designs vs. Fixed Designs

Many requirements from the Simulation Study section not unique to adaptive designs

- Many well established methods exists which do not require extensive simulations to prove protection of type I error rate control, e.g. group sequential designs with SSR
- Assumptions on treatment effects etc. should always be well-founded, and maybe even more so when no adaptation is possible

Heterogeneity over time also not specific to adaptive designs

- Can happen in fixed designs but usually not questioned
- What does „any heterogeneity between stages“ even mean?

Topics Missing From the Guideline

Adaptations to the endpoint(s)

- Adaptations to the test statistic
- Selection of the endpoint, or components of it
- Adaptations to the multiple testing strategy

Adaptations to the adaptive design itself

- Skipping, adding, combining interim analyses

Clearer guidance on pipeline data

- What does it mean that we „should report results from interim analysis and from the analysis based on all available data“?

Helpful Recommendations on Operational Aspects

Operational requirements less subject to change with better knowledge of methodology

Prevention of information leakage as important as ever

- How to prove it did not happen?

Backcalculation of treatment effect from new sample size

- Planning for a fuzzy SSR
- Laying down SSR rules in hidden annex to SAP or IDMC charter
- Hiding new sample size from sites by, e.g. giving country specific targets only

Highlighting importance of independent SSG

Unclear role of sponsor committee

Summary

Guideline is overly focussed on pitfalls, not on opportunities

We as an industry have 20+ years of experience with adaptive designs

- There are many design types which are well established and whose properties can be substantiated on theory, not relying on simulations
- Many of the requirements apply to fixed designs as well

Would appreciate more guidance on, e.g. which opportunities have been missed to date

Sometimes more concrete recommendations would be helpful

- Pipeline data
- Heterogeneity across stages