Platform trials: some considerations from a statistician

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Expertise and role of statistician?

Bayes vs. frequentist?
Does not matter much. See backup.

What really matters:
Exploratory vs. confirmatory.

Exploratory vs. confirmatory

Design aspect	Exploratory	Confirmatory
Primary goal	Estimation	integrity, validity, type I error control
Pre-specification	some flexibility	stringent: considerations like for any Phase 3
Principles to avoid bias	flexibility	randomization / choice of controls, blinding, iDMC
Adaptive design elements	maximal flexibility	stringent: type I error control, advanced statistical methods
Interaction with stakeholders	statistical methods much easier to communicate	potentially difficult interactions
Regulatory-grade		Confirmatory regulatory-grade: type I error control, highest possible standard to run a trial

How does the type of adaptation affect requirements?

What adaptations do we have for confirmatory trials?

Method	Potential adaptation after interim	Reacts to	Key methods
Group-sequential design (futility)	Set sample size to 0	Treatment does not (sufficiently) work	Flexible choice ouf boundary, evaluate OCs
Group-sequential design (efficacy)	Set sample size to 0	Treatment works efficiently	Joint distribution of test statistics
Change allocation ratio	Change allocation ratio	Positive interim result	p-value combination
Blinded Sample size reassessment	Re-estimate sample size	Variance estimate off at design	No type I error inflation, standard analysis
Unblinded Sample size reassessment	Re-estimate sample size	Variance estimate off at design	p-value combination
Treatment arm selection	Drop one or more arms (e.g. low dose)	Different efficacy between arms	p-value combination + closed testing
Enrichment	Decide on testing strategy for final analysis	Different efficacy in subpopulations	p-value combination + closed testing

Frequentist: Doing these under type I error control requires advanced statistical methods.

Bayes:

- First, overall operating characteristic needs to be decided on.
- Computations typically (much) easier.

Control Definitions and Scientific Validity

Questions that need to be answered:

- Do we want type I error control?
- If we have controls (umbrella trial): Internal? External? Randomized? Concurrent? Non-concurrent?
- Further principles to avoid bias: prespecification, blinding, iDMC, independent response review.

References

Dragalin, V. (2006). Adaptive designs: terminology and classification. *Drug Inf J*, **40**, 425–435.

Thank you for your attention.

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Backup

Bayes vs. frequentist

Design aspect	Frequentist	Bayes
Basic statistical concepts	Same	
Principles to avoid bias: randomization / choice of controls, blinding, iDMC, pre-specification	Same	
Adaptive design elements (if confirmatory)	frequentist adaptation theory	very much depends on requirements
Interaction with stakeholders	Same	
Need for simulations	Same	
Bayes methods	Basic understanding	Prior specification, Bayesian computation

Frequentist vs. Bayes less important distinction than confirmatory vs. exploratory.

Definitions

Adaptive design, as defined in E20 draft: Clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on interim analysis of accumulating data from participants in the trial.

Validity:

- Provide valid statistical inference (adjusted p-values, unbiased estimates, adjusted confidence intervals, etc.),
- ensure consistency between different stages of the study,
- minimize operational bias.

Integrity:

- Provide convincing results to a broader scientific community,
- preplan as much as possible based on intended adaptations,
- maintain blind of interim results.

See Dragalin (2006).

R version and packages used to generate these slides:

R version: R version 4.4.3 (2025-02-28 ucrt)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages:

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