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Considerations behind the Reflection Paper on Confirmatory Trials with an Adaptive Design

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The views expressed in this paper are those of the author and not necessarily those of the BfArM

Introduction – we had been happy then?

Interim analyses are often an ethical mandate:

- even after sound research in phase II sufficient uncertainty about treatment effects will often remain at the beginning of phase III.

Group sequential designs

- had been developed to avoid inflation of the type-I-error associated with repeated testing of accumulating data,
- allow for a rather flexible number and timing of interim analyses,
- allow to stop the trial early for efficacy or futility.

Why did we need more?

- wish to increase sample size

Introduction – unlimited opportunities:

Landmark paper:

- P. Bauer and K. Köhne: Evaluation of experiments with adaptive interim analyses. Biometrics 50:1029-1041, 1994.

- *Idea:* understand study as a “pre-planned meta-analysis” of two sub-studies;
- *Flexibility:* because only P-values from stages are combined in the end;
- *Simple decision rule:* type 1 error is controlled at 2.5% (one-sided) if $P_1 \times P_2 < 0.0038$.

Introduction - expectations are high:

Confirmatory research:

- areas of decision-making (e.g. drug licensing), where existing hypotheses require independent replication / confirmation.

Adaptive design:

- clinical trial allowing design modifications while the trial is ongoing without compromising the pre-specified type-I-error.

Integrity of a trial:

- a state where a clinical trial is without major inconsistencies that prevent from results being readily interpretable.

Is there a need to limit flexibility?

Early imagined “Viagra-type” examples:

primary endpoint	*Treatment*	*Control*	*Risk Diff. 95% CI*	*P-Value (1-s)*
Angina responder (stage 1)	249/631 (39,5%)	228/645 (35,4%)	4,1% (-1,2%; 9,4%)	0,064
Sexual function responder (stage 2)	30/62 (48,4%)	24/69 (34,8%)	13,6% (-3,3%; 30,5%)	0,056

$P = P_1 \times P_2 = 0{,}00358$

Is it OK to reverse the burden of proof?

Results from a bipolar disorders trial:

Part	Mean (N)	Mean (S)	Sample Size	P-Value (1-sided)
1st part	-13,46	-11,45	59/58	0.1385
2nd part	-13,27	-9.95	38/43	0.0457
3rd part	-13.32	-8.46	28/22	0.0546

What, if such a result had come up after an interim analysis with a design modification?

Adaptation of design specifications:
Minimal requirements and general principles

- control of a pre-specified type-I-error,
- availability of corresponding methods to estimate a treatment effect and a confidence interval with correct coverage
- the additional identification problem must be addressed (differences in effects due to chance / communication of interim results / design change?)
- it is not upon regulators to question homogeneity (sponsors must justify combinability)
- the body of evidence that justifies the treatment recommendation must be identifiable (rejection of an intersection null-hypothesis may not be sufficient, no small steps)
- too many design modifications question the confirmatory nature of the trial

Role of adaptive designs and of the guideline

Adaptive designs can be used:

- to rescue a trial with problems
- to pre-plan ways to cope with difficult reality

Obviously it is the latter which is of interest in confirmatory research!

Role of the reflection paper is

- not, to limit research in experimental design;
- to address issues that may complicate the interpretation of trial findings so that they can be discussed upfront (and not post-hoc);
- to openly discuss regulatory assessment strategies;
- to acknowledge that based on limited experience only cautious advice can be given.

Discussion

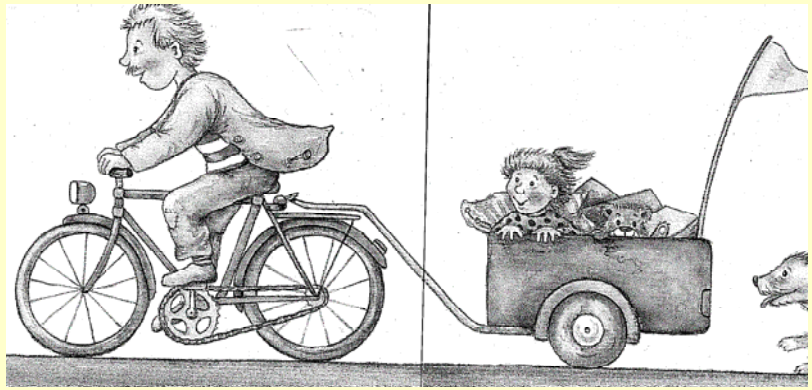
In some instances studies can be planned with a flexible or adaptive design involving design modifications based on the results of interim analyses.

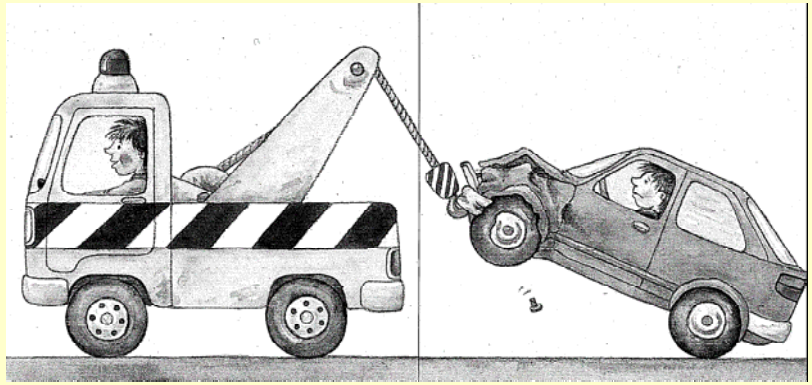
Such a design can speed up the process of drug development or can be used to allocate resources more efficiently without lowering regulatory standards.

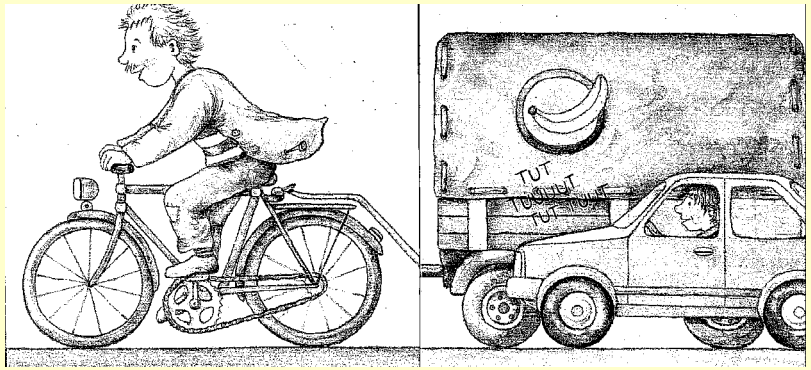
This is especially welcome if at the same time the basis for regulatory decision-making is improved.

In all instances the type of the anticipated design modification (change of sample size, discontinuation of treatment arms, etc.) would need to be described and justified in the study protocol…

Summary







Door is open, use it carefully.
Good examples are needed!