BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

European perspective: the *emea* reflection paper

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Views expressed in this presentation are those of the author and not necessarily those of the BfArM or the Scientific Advice Working Party at the emea

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 $P_1 \times P_2 < 0.0038$.

Adaptive designs:
Where is the need for correction?

Sample size not correct:

"Response" differs from expectation.

Endpoint not OK:

Composite endpoint not sensitive; treatment effect in an other variable than expected; wrong definition of responder.

Want to change the aim:

Maybe, proof of superiority was too ambitious.

and:

Changes in criteria for in-/ex-clusion

Wrong dose or treatmnet

Inappropriate documentation

Statistical methodology only suboptimal

The game:
Adaptive designs in late stage drug development

"The purpose of phase III is to confirm the findings obtained so far in pre-clinical studies, tolerance studies, dose-finding and other phase II studies."

(CPMP/EWP PtC on (i) meta-analysis
and (ii) one pivotal trial)

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?

Unlimited opportunities?

From the original paper by Bauer & Köhne:

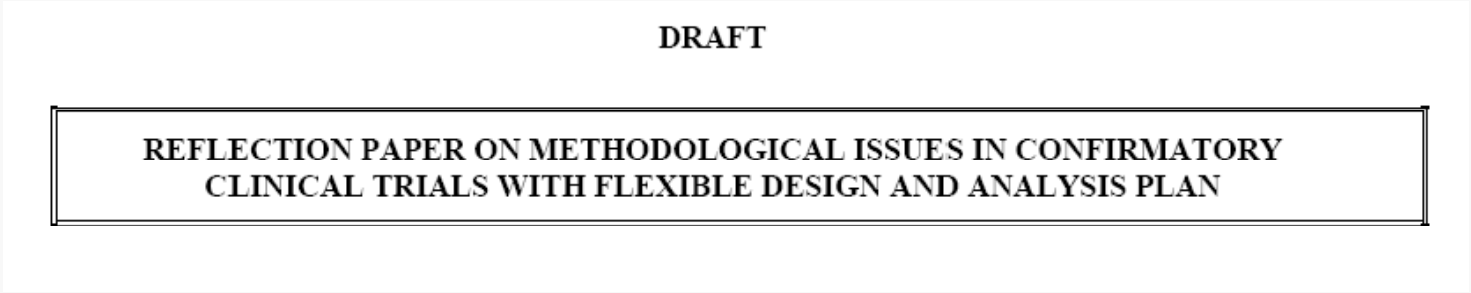
"Hence even the reduction in the number of components of a multiple endpoint may be a desirable goal for a protocol adaptation…"

"Finally it has to be mentioned that the interim analysis may result in strong grounds for completely redesigning the trial…."

cautious remark:

"If only the sample-size is open to adaptation, the interpretation of the decision rule is simple …However, if the intersection hypothesis is rejected in the final global analysis this would lead to the acceptance of the respective alternative … The resulting problem of the interpretation is the price to be paid for changing essential features of the design.

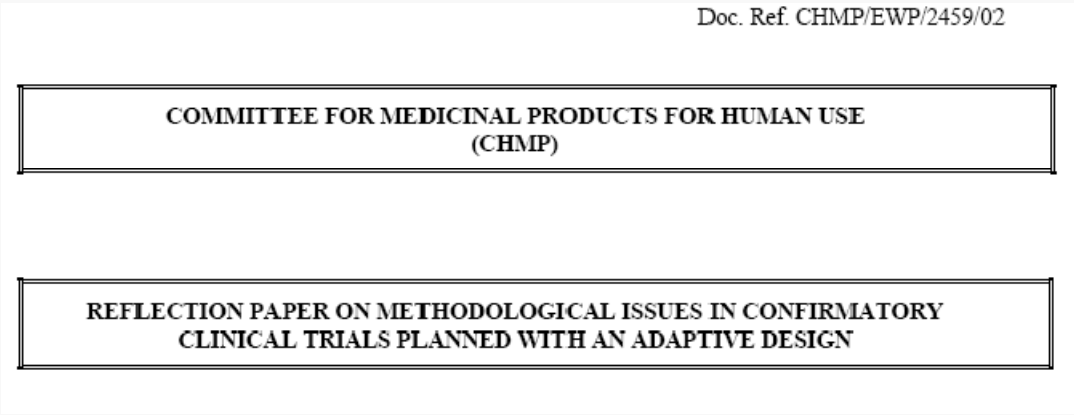
Reflection paper -
discussion about adaptive designs in *confirmatory* trials:



DRAFT

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS WITH FLEXIBLE DESIGN AND ANALYSIS PLAN

– has been out for consultation, received many useful comments, and is now finalized:



Doc. Ref. CHMP/EWP/2459/02

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN

available from:

http://www.emea.europa.eu/pdfs/human/ewp/245902enadopted.pdf

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.

Specific comments about adaptations:

Sample-size recalculation:

- least controversial issue, but: preference given to blinded SSR-methods

Change or modification of primary endpoint:

- PE should reflect patient benefit; difficult to argue after the fact, that something should no longer be relevant

Ph II/Ph III-combination and dropping of arms

- identification problem: what, if population and estimate for the treatment effect change? Replication-issue!

Switching:

- a non-issue

Modification of essential design features

- identifiable body of evidence required for licensing

Specific comments about adaptations:

Number of stages of an experiment:

- why a second sample size recalculation?
- how to justify another change in an essential design feature?

Fact is:

- Too many changes make the trial exploratory

Compromise:

- Clearly describe uncertainty at the beginning of phase III and foresee the option for some few design changes

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…

(intro of the reflection paper)

Summary