European regulatory perspective on flexible designs

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The views expressed are personal views and not necessarily the views of CBG-MEB or EMA

Key reflections

- Which principles underly both EMA and FDA Guidance?
- Some considerations when confirmatory trials with an adaptive design are assessed.
- Where could there be different approaches at present?
- Emerging challenges.

Principles underlying EMA / FDA Guidance

European Medicines Agency

London, 18 October 2007
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

To argue for design modifications in a phase III trial……is…….a contradiction to the confirmatory nature of such studies…….

A study design is called *"adaptive"* if statistical methodology allows the modifcation of a design element (e.g., sample size, randomisation ratio, number of treatment arms) at an interim analysis with full control of the type I error.

Principles underlying EMA / FDA Guidance

- Maintaining trial integrity in case of interim analyses (*comparative analyses).*
- For confirmatory trials: control of Type I error.
- Pre-planning and full pre-specification of adaptations.
- Estimation of treatment effects (benefit-risk).

Potential benefits acknowledged in changing landscape.

Considerations

Maintaining trial integrity is a challenge, *that increases with the number of adaptations considered*.

In a trial with a GSD (O'Brien Fleming type), double-blind with independent DSMB and independent statistician:

- Recruitment in a few sites was stopped early by sponsor (not an uncommon adaptation in trials).
- At assessment it becomes clear effect sizes in these sites was negative.
- From presentations made to the DSMB it could possibly be re-constructed what the impact of the treatment effect per site was.
- It could not fully ascertained that sponsor did not have any view on the respective part of presentations made to DSMB.

Considerations trial integrity

Comparative interim analyses and associated *planned* adaptions can also impact the uncertainty on effects of *unplanned* adaptations, that otherwise would be relatively unproblematic.

“Burden of proof” of trial integrity likely to increase with number of adaptations.

Considerations

The type I error is an imaginary quantity

- Associated with “decision procedure”, based on the design and a specific statistical model.
- Which we (have to) agree to be plausible before the data are collected.

Control

- Has brought us many good things to achieve reliable confirmatory trials.

- **Could be seen as threshold for *proceeding to secondary assessment***

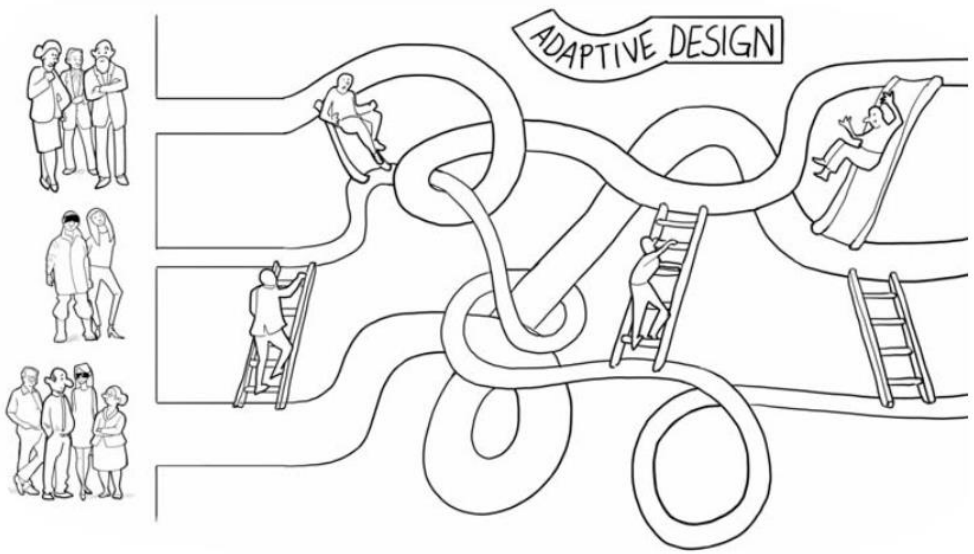
Also secondary analyses need to be understood for adaptive trials.

Considerations

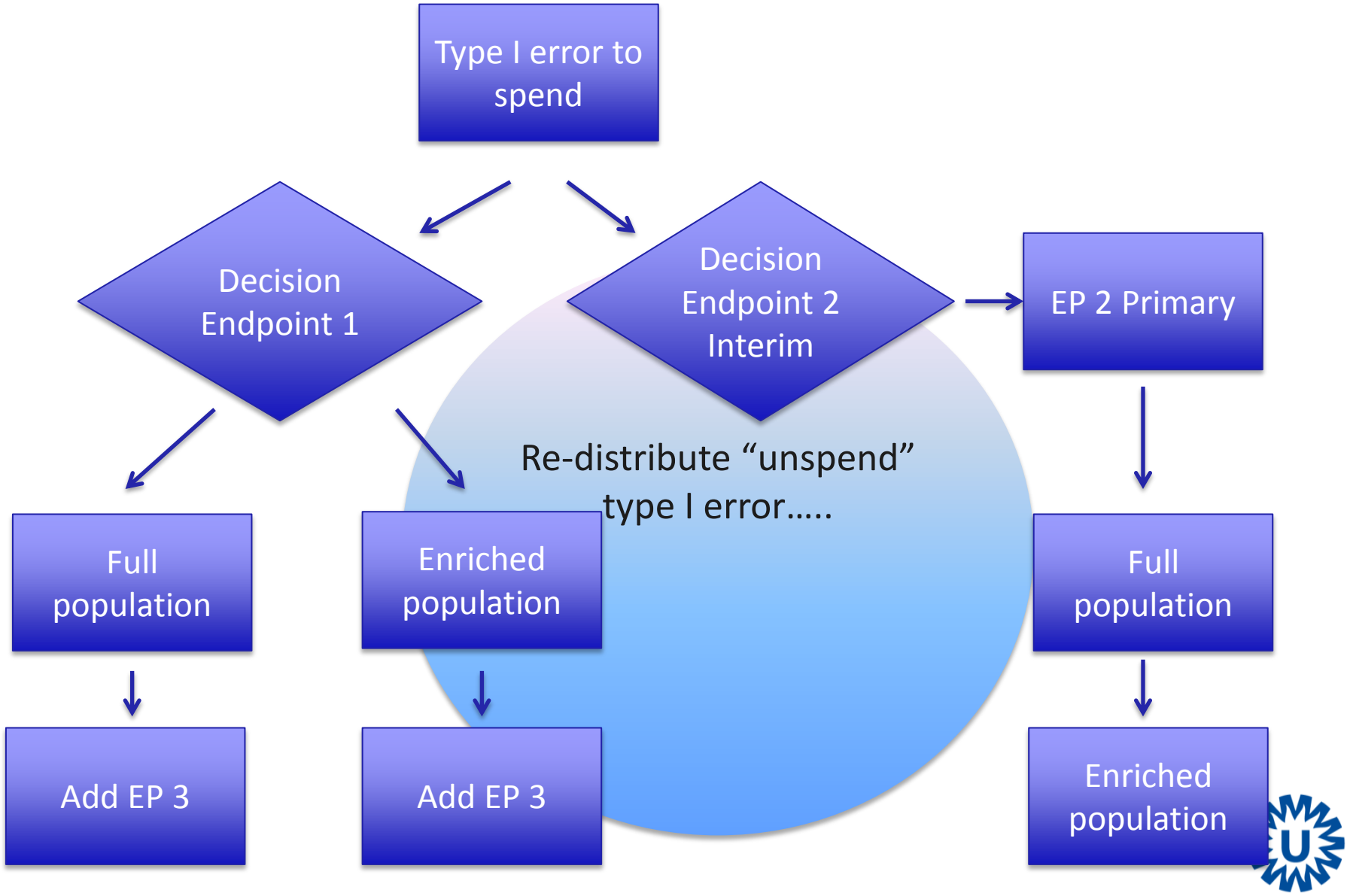
Regulatory assessment ..... Relatively uncomplicated for confirmatory trials with:

- Group sequential design
- Sample size adjustments

But this is not (always) what we see.....



Considerations



Considerations primary and secondary assessment

- Usually type I error control resolved at Scientific Advice stage.
- Benefit-risk includes *residual uncertainty*: May still turn assessment negative.
- Estimation not as prominent in a priori discussions.
  - Will/needs to change with E9(R1) on **estimands**!
  - Methodology not always there.
- Secondary assessment more attention needed:
  - Robustness of effects across **subgroups**, endpoints,….
  - Safety aspects.
  - Methodology needs development.

Different approaches (in light of ICH E20)?

- EMA Reflection Paper strongly focuses on confirmatory trials.
- Control of type I error.
  - Simulations are valued by both agencies.
  - Stronger preference for analytical assessment at EMA
- Perspectives and regulations on role of Data Monitoring Committees, and other (potential) bodies.
- The emphasis on estimation and clinical endpoints at assessment.

Emerging challenges

- Adaptive features combined with additional “challenges”:
  - Master protocols, shared control groups.
  - Single arm trials and external controls.

- More flexible clinical development plan strategies:
  - Decisions to submit early (not await the planned Phase III results).
  - What used to be Phase II attrition risk may become part of regulatory residual uncertainty.

- Emerging therapies (targeted, advanced medical therapy,..):
  - Different perspective on designs for efficacy and safety.

Regulatory interaction

- Early and intensive (Scientific Advice through all stages).
- Would love never having to read again (as it does not ask for Advice):

  "Does the agency agree……."

- More focus and discussion on entire clinical development strategy (also exploratory trials)
  - Taking into account potential **adaptive** nature of the **clinical development plan**.