Introduction to Adaptive Clinical Trial Designs

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“FDA Signals It’s Open to Drug Trials That Shift Midcourse”

Ways adaptive designs may allow trials to be adjusted based on early results:

- Route a larger share of patients to the treatment that seems to work best
- Drop treatments that don’t seem to be effective
- Add more of the type of patients . . . reacting best to a particular treatment
- Merge two different phases of drug development into one trial

With views from:

Bob O’Neill , FDA

Paul Gallo, Novartis

Tom Fleming, Univ. Washington

Michael Krams, Wyeth

Don Berry, M. D. Anderson Cancer Center

Bruce Turnbull, Cornell University

1. Motivation for adaptation in clinical trials

Adaptation to external factors

Changes in the clinical setting or economic background

Following withdrawal of a competing treatment, a smaller treatment effect is now of clinical interest.

An improved financial position means sponsors can invest more in this trial.

Adaptation to internal factors

Nuisance parameters affecting sample size

In-study estimates of sample variance indicate a greater sample size is needed to achieve the intended power.

Overall failure rates in a survival study are low: higher accrual and longer follow-up are required.

Adaptation in clinical trials

Adaptation to internal factors . . .

Safety outcomes

Higher than expected toxicity implies treatment dosage should be reduced.

A lower rate of adverse events in the experimental treatment suggests it will suffice to demonstrate non-inferiority, rather than superiority.

Sub-group analyses

Treatment benefits a particular sub-group: investigators wish to re-define the target population.

Change of endpoint

An alternative endpoint provides better discrimination between treatment groups: investigators wish to re-define the primary endpoint.

Adaptation in clinical trials

Adaptation to internal factors . . .

Response on primary endpoint

Results on the new treatment are good and it is desirable to reach a conclusion as rapidly as possible.

Responses on the new treatment are not so good: investigators wish to increase sample size for power at a lower effect size than originally planned.

Response-dependent treatment allocation

Interim data suggest one treatment arm could be superior but results are not yet statistically significant. To improve treatment of patients in the trial, weight random allocation in favour of the currently superior treatment arm.

Adaptation in clinical trials

A trial with multiple treatments or dose levels

Eliminate weaker treatments as the study progresses.

Using a dose-response model, optimize treatment allocation in order to learn most efficiently about the best choice of dose level.

Combining Phase IIb (dose finding) and Phase III (confirmatory trial)

Select the best dose level in Phase IIb.

Proceed directly to Phase III and test the treatment at this dose level, eliminating “white space” between phases.

Combine Phase IIb and Phase III data in the final statistical analysis.

Possibly use a more rapidly available surrogate endpoint in Phase IIb.

Optimize the allocation of resource between Phase IIb and Phase III.

2. Adaptivity and flexibility

Rigid adaptive designs

Adaptivity does not necessarily imply flexibility.

Rules for adaptation can be completely specified in the protocol and implemented as such, with the advantages:

- Potential modifications are approved up front by FDA, ethics committees, and the DSMB.
- There is no need to file protocol amendments.
- Logistics for changing treatments, patient eligibility, accrual rates, etc., can be planned for in advance.
- Credibility of results is maintained, especially with the DSMB as a “firewall”.
- *Statistical benefits:* The final analysis can depend on sufficient statistics.
  A well-defined sampling frame aids frequentist point and interval estimation.

Adaptivity and flexibility

Totally flexible designs

After setting up a suitable global framework, design modifications can be made at interim analyses without prior planning.

L. Fisher (*Biometrics*, 1998) refers to the “self-designing” clinical trial.

- Advantages
  - Investigators can learn about treatments and respond appropriately.
  - Complete flexibility to react to un-anticipated occurrences.
- Disadvantages
  - Ad hoc changes based on unblinded data may jeopardise credibility.
  - Test statistics of an unfamiliar form:

    can be a source of inefficiency (Jennison & Turnbull, *Biometrika*, 2006),

    may lead to anomalous results (Burman & Sonesson, *Biometrics*, 2006).

Adaptivity and flexibility

Partially flexible designs

A compromise solution is to provide flexibility for re-design within a clearly stated framework.

Example: Bauer & Köhne (*Biometrics*, 1994) two-stage design

- Design and length of Stage 1 are fixed in advance.
- The design of Stage 2 is permitted to depend on Stage 1 results in an arbitrary and unplanned way.
- Final inference is based on P-values from the two stages, according to a pre-specified rule.
- Multi-stage designs can be constructed by applying the method recursively.

3. The regulatory view

ICH E9 favours prior planning, clearly documented at the outset:

> "A confirmatory trial is an adequately controlled trial in which the hypotheses are stated in advance and evaluated."
>
> "Deviations from the planned procedures always bear the potential of invalidating the trial results."
>
> Experimenters should think in advance about " . . . the way in which anticipated analysis problems will be handled."

Nevertheless, the possibility of modifying an ongoing trial is acknowledged:

> "If it becomes necessary to make changes to the trial, . . . changes to the statistical procedures should be specified in an amendment . . . discussing the impact on any analysis and inferences that such changes might cause.
>
> The procedures selected should always ensure that the overall probability of Type I error is controlled."

The regulatory view: FDA

The FDA has indicated a supportive attitude to adaptive designs:

> " . . . the advantages of these [adaptive] approaches, rigorously designed, are becoming more evident, including among the ranks of our experts at FDA. It is essential that we at the FDA do all we can to facilitate their appropriate use in modern drug development."

> " . . . the FDA's drug center is working on a series of guidance documents — up to five in all — that will help articulate the pathway for developing adaptive approaches to clinical trials."

These quotes are from the speech by Scott Gottlieb, MD, the FDA's Deputy Commissioner for Medical and Scientific Affairs, before the July 2006 Conference on Adaptive Trial Design, Washington, DC. See also

`http://www.fda.gov/oc/speeches/2006/trialdesign0710.html`

A more cautious regulatory view: EMEA

European regulators have taken a more sceptical stance:

> "We are reluctant to support the view that more and more decisions regarding design issues and statistical methodology can be deferred to later phases . . . of the trial. This may not be beneficial for trial quality in general."

> "The high credibility of the results from randomised clinical trials . . . is not exclusively a direct consequence of randomisation, but stems from the need to carefully pre-plan the scientific investigation."

> "We strongly believe that adaptive designs have a place in phase III but hope that this place will be explored carefully in order to avoid exaggerated expectations that cannot be fulfilled . . . "

Source: Armin Koch, Federal Institute for Drugs and Medical Devices, Bonn, Germany (*Biometrical Journal*, 2006, p. 11).