Adaptive design of Clinical Trials

“Musch ado about nothing?”

Pieter Neels, MD

Independent Regulatory Expert

Ex- CHMP member for Belgium

Ex- Vice-chair VWP (EMA)

Disclaimer

- Although I have been a member of the CHMP, my presentation might not be the view of the CHMP, the European Medicines Agency (EMA), the Belgian Medicines Commission, neither of the Vaccine Working Party.

- My presentation is a personal viewpoint and binds in no way the organisations mentioned before.

Declaration of interest

I have signed consultancy contracts with more than 100 organisations and companies under which

- WHO
- B&MGF
- Universities of Antwerp, Ghent, Leuven, Namur, Brussels, Paris, Lausanne, Köln, …
- Big pharma
- Medium pharma
- Small pharma

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Sources

Regulatory guidance documents:

- **EMA:** Methodological issues in confirmatory clinical trials planned with an adaptive design - Scientific guideline https://www.ema.europa.eu/documents/scientific-guideline/reflection-paper-methodological-issues-confirmatory-clinical-trials-planned-adaptive-design_en.pdf
- **FDA:** Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry

Sources (2)

A number of interesting articles (open access):

- **EMA article:** https://doi.org/10.1186/s13063-018-3012-x

  Adaptive designs in clinical trials: from scientific advice to marketing authorization to the European Medicine Agency
- Deepak_NEJM_Article on adative design: N Engl J Med 2016;375:65-74. DOI: 10.1056/NEJMra1510061

  Adaptive Designs for Clinical Trials
- european-federation-pharmaceutical-industries-associations-second-workshop-adaptive-design_en https://www.ema.europa.eu/en/documents/minutes/minutes-european-medicines-agency/european-federation-pharmaceutical-industries-associations-second-workshop-adaptive-design_en.pdf
- Mahajan_India_Article on adaptive design: Adaptive design clinical trials: Methodology, challenges and prospect doi: 10.4103/0253-7613.68417: 10.4103/0253-7613.68417

Sources (3)

A number of interesting articles (open access):

- **Thorlund_Canadian_Article on adative design:** Key design considerations for adaptive clinical trials: a primer for clinicians

  Cite this as: BMJ 2018;360:k698 http://dx.doi.org/10.1136/bmj.k698
- White Paper_ Understanding Adaptive Designs for Clinical Trials _ NSF https://www.nsf.org/knowledge-library/white-paper-understanding-adaptive-designs-for-clinical-trials
- WHO_COVID-19_IMI

  https://www.imi.europa.eu/news-events/newsroom/whos-covid-19-clinical-trial-adaptive-what-does-mean

Introduction

What is the definition of Adaptive Design Clinical trials?

Adaptive design, as defined by the U.S. FDA, is “a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.”

Adaptive design characteristics include modifying an ongoing clinical trial in accordance with predetermined rules, based on data from interim analyses. Adaptive design allows for greater flexibility in clinical trials with benefits of adaptive design trials, or adaptive clinical trials (ACTs), including increased efficiency, better ethical protections, greater generalisability/understanding of drug effects and higher approval from sponsors.
Overall, adaptive designs make better use of resources when conducting clinical trials.

Introduction (2)

Concerns Regarding Adaptive Designs

The use of adaptive designs in clinical trials has been hindered by

- inexperience of researchers,
- fear from stakeholders and regulatory bodies, and
- practical limitations and challenges of some adaptive design types.

Inexperience

Inexperienced researchers do not understand the added complexities of adaptive designs. Knowing when and when not to adapt a trial, how to strategically plan for logistical challenges and how to conduct complicated interpretations are skills of the expert biostatistician, not the novice.

Fears From Stakeholders and Regulators

Changing rules in an ongoing trial creates complications and uncertainty, which can be intimidating to stakeholders and regulators. Lack of familiarity with new methods leads to conservative decision-making (e.g. choosing familiar RCTs over ACTs).

Introduction (3)

Concerns Regarding Adaptive Designs (2)

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Practical Limitations/Challenges

Special analytical methods are required to avoid increased chances of erroneous conclusions and bias, and for some design types, methods are not available to account for these increases.

Efficacy gains can cause losses in other areas of a trial. Designing an adaptive trial takes more time than designing a traditional RCT, which can delay the study start.

By adding modifications, logistical challenges arise and must be overcome to ensure trial conduct and integrity are preserved.

Results gained from adaptive trials can be too specific to generalise, or lead to interpretability challenges.

Introduction (4)

Addressing Adaptive Design Challenges

To address the challenges associated with adaptive designs, the following four principles are suggested to consider during the clinical trial design stage:

1. Control for the chance of erroneous conclusions by addressing possible Type I error probability inflation. Statistical theory can be utilized as well as simulations that evaluate the chance of erroneous conclusions.

In statistics, a Type I error is a false positive conclusion, while a Type II error is a false negative conclusion.

Example: Type I vs Type II error
You decide to get tested for COVID-19 based on mild symptoms. There are two errors that could potentially occur:
Type I error (false positive): the test result says you have coronavirus, but you actually don't.
Type II error (false negative): the test result says you don't have coronavirus, but you actually do.

Introduction (4)

Addressing Adaptive Design Challenges

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1. Control for the chance of erroneous conclusions by addressing possible Type I error probability inflation. Statistical theory can be utilized as well as simulations that evaluate the chance of erroneous conclusions.
2. Bias in estimating treatment effects should be evaluated and available methods for adjusting estimates should be applied to reduce or remove bias whenever possible. If methods are unavailable, appropriate cautions to interpretation should be noted.
3. Adaptive design trial details should be specified prior to trial conduct, and documented in the study protocol. It is important that all adaptions are completely specified to ensure trial integrity, maintain safety, minimize access to comparative interim data and control for erroneous conclusions.
4. Trial conduct and integrity should be maintained by predicting, and setting up safeguards to prevent, possible trial conduct issues. Controlled access to information should be addressed in this plan.

Adaptive design

Examples*:

- Three case studies are given in the EMA/EFPIA workshop report:
  1. Eli Lilly, phase II/III in type 2 diabetes
     - Adaptive design concerned the dose of the new product
     - Randomisation in 9 groups:
       - Placebo and one active control
       - 7 different doses
     - If after the predefined interim analyse a dose can be selected, next part of the trial will continue with this dose.
  2. Novartis presented a phase II/III trial in chronic disease.
     - 7 groups were tested in the adaptive design part of the trial:
       - 1 placebo and 2 active controles
       - 4 different dose groups of the new product
     - After the pre-planned interim analysis, decision was made whether the sponsor would continue and with which dose
  3. Wyeth presented the third case in acute migraine attack
     - Again a 2 phase approach to determine the optimal dose
     - 192 would be randomised to test 7 different doses plus active control and a placebo

Adaptive design

What do we learn?

- Most adaptive design trials work on dose
- Time gain: is clearly in setting up of the trial: seamless continuation from phase II in phase III
- In vaccinology, time gain could be earlier:
  - As Phase I can be used to determine the immunogenicity of a given dose of antigen and/or adjuvant, an adaptive design phase I/II is attractive
- But don't underestimate the work:
  - Setting up of a 10-arm phase I/II with interim analysis will take time and you need experienced people
  - Decision making on the interim analysis: you need experienced people
  - Adaptive design will need clear discussion with regulators before submission of the CTA

Adaptive design

An example in the vaccinology:

- A new vaccine against Shingles with a recombinant antigen plus a novel adjuvant
- Phase III study (accepted by EMA) will be an immunobridging against GSK Shingrix
- The crucial question is: what is the optimal dose of both antigen and adjuvant.
- The FIH* could be done in a 10-arm setting (or even more) with an adaptive design, from phase I to phase II exploring the right dose of antigen and adjuvant:
  - 1 placebo and one active control (Shingrix)
  - Different antigen and adjuvant combinations
- The interim analysis will give the optimal combination and in phase II, and so 1, or 2 combinations can be further tested on safety and immunogenicity preparing the optimal dose for the phase III.

*First in Human (phase 1 trial)

Conclusions

Adaptive design is a major step forward in medicinal product development, but…

- **This technique is based on pro-actively thinking and writing: all possible decisions should be written in the protocol**
- **Time gain lies primarily in defining the right dose**
- **We need experienced people:**
  - **To write the protocol**
  - **To set up the decision criteria**
  - **Take the decisions**
  - **Execute the CTA's**
- **Information exchange with regulators is crucial**
  - **EU & US are on the same page: guidance documents are quite similar.**

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