Options for confirmatory adaptive designs involving treatment selection

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Outline

- Background
- Description of confirmatory seamless adaptive designs
- Different approaches to such designs in the case of treatment selection
- Practical Examples
- Conclusions

Traditional Drug Development

Phase II trials

- **Early** trials to assess treatment efficacy
- **Exploratory** - error rates not tightly controlled
- **Select** one of several treatments/doses for further development and define hypotheses / populations of interest

Phase III trials

- **Large-scale** controlled trials
- **Comparison** of a single experimental treatment with control
- **Confirmatory** - error rates controlled to give definitive conclusions

Confirmatory seamless adaptive designs

- Combine phases II and III into a single trial
- Conduct the trial in several stages
- Early stages: Main objective is to refine the questions / hypotheses for further study
- Later stages: Definitive evaluation of hypotheses of interest

Advantages/disadvantages

Advantages

- Eliminates the delays between the two phases
- Efficiency gains from using the phase II data in an overall analysis at the end of phase III
- Write a single protocol and seek ethical and regulatory approval once
- If the final outcome is a successful trial, the sooner this is discovered the better

Disadvantages

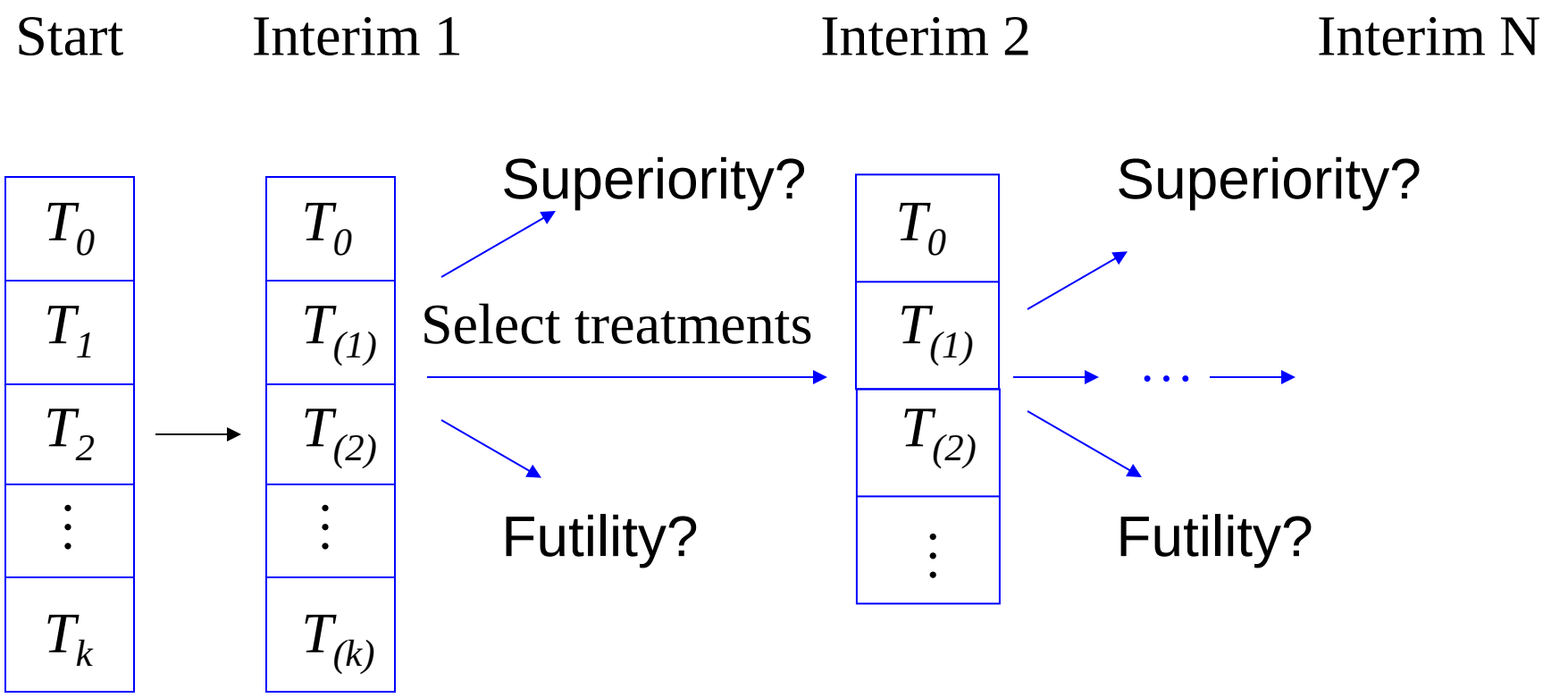
- Loose the “thinking time” between the two-phases
- Positive results in a separate phase II trial will help recruitment for phase III
- Have less total experience of treatments in use by patients
- Loss of independent replication of the results

Scenarios for confirmatory seamless adaptive trials

- Majority of work has focussed on treatment selection designs. Main objective of early stages is to select promising treatment(s) for further study. Later stages compare selected treatment(s) with control

- NOTE: Another context of increasing interest is subpopulation selection. Early stages would identify the (sub)populations for further study. Later stages would evaluate treatment in the chosen (sub)populations [not discussed here]

The General approach: Treatment Selection



T_0: Control Treatment $T_1, \ldots, T_k$: Experimental Treatments

Approaches to Design

AIM: Control Family Wise Error Rate (FWER) allowing for selection/multiple testing

Combination test method

- Tests hypotheses using the p-values from various stages and combining them appropriately

Group sequential designs

- Based on cumulative sufficient statistics

Conditional error function approach

- Uses the work of Müller and Schäfer

Combination test designs

We want strong FWER control

Start with several elementary hypotheses H_i

Define $H_I = \bigcap_{i \in I} H_i$

to be all possible intersection hypotheses involving H_i

- Use closed testing methods together with the combination test approach of *Bauer & Köhne (1994)*

Make use of Closed testing procedure

Marcus et al. (1976)

Reject H_i if and only if reject H_I for all I with $i \in I$

This controls FWER in strong sense

Employ the Combination test

Get p_{Ij}: p-value for testing H_I based on stage j data

Combination p-value for testing H_I *(2 stage case)*:

$$C(p_{I1}, p_{I2}) = 1 - \Phi(w_1 \, \Phi^{-1}(1 - p_{I1}) + w_2 \, \Phi^{-1}(1 - p_{I2}))$$

Lehmacher & Wassmer (1999)

Test each H_I using combination test p-value

Maintains error rate provided

p_{I1} and p_{I2} satisfy the (asymptotic) p-clud condition

Brannath et al. (2002)

Some Example Literature

- Treatment selection based on a single endpoint: *Bauer & Kieser (1999); Bretz et al. (2006)*

- Treatment selection with a change of endpoint: *Friede et al. (2011)*

- Incorporation of Bayesian techniques to make the selection: *Schmidli et al. (2007); Brannath et al. (2009); Kimani et al. (2009)*

Group sequential design

- At the j^{th} look calculate cumulative test statistics based on **all** data up to and including look j relating to a particular hypothesis indexed by i

e.g. S_{ij}: efficient score statistic for H_i

I_{ij}: observed Fisher's information for H_i

Assume that $S_{ij} - S_{ij-1} \sim N(\theta_i (I_{ij} - I_{ij-1}), (I_{ij} - I_{ij-1}))$

- See *Jennison & Turnbull (2000)*

Stopping Boundaries

Determine stopping boundary values u_j and ℓ_j via e.g. use of a *spending function*

(*Lan & DeMets (1983)*)

Stop if $S_{ij} \geq u_j$ or $S_{ij} \leq \ell_j$

Stop at the K^{th} look if not before

Note: As earlier data also contribute to later analyses, the test statistics themselves are correlated

Some Example Literature

- Treatment selection where the best treatment is selected at the first interim based on a single endpoint: *Stallard & Todd (2003)*

- Selection of a pre-specified number of treatments at each stage: *Stallard & Friede (2008)*

- Selection where the number of treatments is not fixed in advance: *Magirr et al. (2012)*

- Treatment selection based on short-term data: *Todd & Stallard (2005)* or short- and long-term data: *Stallard (2010)*

Conditional Error function approach

- At an interim analysis calculate the probability of rejecting the null hypothesis given it is true conditional on the data observed – conditional error
- Design can then be modified provided the critical value of the next stage is adjusted so as to ensure that this conditional error remains unchanged
- This procedure protects the overall type I error rate
- An extension of the work of *Müller & Schäfer (2001)*

Some Example Literature

- Treatment selection with a single endpoint: *Koenig et al. (2008)*

- Treatment selection specifically in the case of time-to-event data: *DiScala and Glimm (2011)*

So which to choose?

- Largely depends on familiarity with methodology, validity of assumptions, acceptability to regulators, ease of implementation, statistical properties
- Combination test & conditional error function approach potentially have more flexibility in terms of adaptations possible compared to the group-sequential approach
- Group-sequential and conditional error function approaches rely on asymptotically normal test statistics
- Combination test and group-sequential methods extend naturally to more than two stages.

Adaptive seamless designs in practice

- Pharmaceutical trials

  INHANCE trial – COPD

  HORIZON III trial - oncology

  Cuffe et al. “When is a seamless study desirable? Case studies from different pharmaceutical sponsors” Pharmaceutical Statistics 2014, 13: 229-237

- Public sector trial

  PROVE trial - osteoporosis

  Barker et al. “Physiotherapy Rehabilitation for Osteoporotic Vertebral Fracture (PROVE): study protocol for a randomised controlled trial” Trials 2014, 15: 22

INHANCE trial

- β-agonist treatment (Indacaterol) for COPD
- Good previous data from dose ranging studies
- Additional dose investigation required because characteristics of the treatment powder changed during scaling up of production

- Two stage design

  Stage 1: 4 Indacaterol doses (75, 150, 300, 600 μg), Placebo, 2 active controls (Formoterol and Tiotopium)

  Stage 2: 2 consecutive doses of Indacaterol, Placebo, 1 active control

INHANCE trial

- Two endpoints
  - Stage 1: Trough FEV-1 at week 2
  - Stage 2: Trough FEV-1 at week 12

- Independent DMC reviewed stage 1 data and were given a set of dose-selection guidelines

- INHANCE has been included as a pivotal study in submission to health authorities globally and drug has been approved

HORIZON III trial

- Oral vascular endothelial growth factor (VEGF) treatment (Cediranib) for metastatic colorectal cancer. Two doses versus active control
- One of three related studies (HORIZON I – Phase II, HORIZON II – Phase III placebo controlled trial)

- Two stage design

  Stage 1: 2 Cediranib doses (20, 30 mg), active control (Bevacizumab)

  Stage 2: 1 dose of Cediranib, active control

HORIZON III trial

- Two endpoints
  - Stage 1: Response rate
  - Stage 2: Progression-free survival

- Independent DMC reviewed stage 1 data and were given go / no-go criteria

- HORIZON III was completed, but was not significant

PROVE trial

- Three management strategies for patients with osteoporosis and a clinically diagnosed vertebral fracture
- Three separate treatments, not different doses

- Two stage design

  Stage 1: Usual care (single session of education and advice), seven individual exercise-based physiotherapy sessions, seven individual manual therapy-based physiotherapy sessions

  Stage 2: One or both physiotherapy arms and usual care

PROVE trial

- Two endpoints
  - Stage 1: QUALLEFO 41 score at 4 weeks
  - Stage 2: QUALLEFO 41 score at 12 weeks

- Independent DMC reviewed stage 1 data and were given quantitative guidelines

- PROVE is ongoing

Conclusions

- Research continues on the open questions surrounding confirmatory adaptive seamless clinical trial designs
- Adaptive seamless clinical trial designs (in the broadest sense) have proved to be effective in several clinical research areas
- To really bring the this methodology into practice needs further work in all aspects – both methodological and practical