Adaptive Trial Designs

Potential obstacles and possible solutions – case studies of adaptive design implementation

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Please do not reproduce
Adaptive trial designs

- “The wise *adapt* themselves to circumstances, as water moulds itself to the pitcher.”
  
  *Chinese proverb*
Acknowledgements

- **Key references**
  - PhRMA Adaptive Designs Working Group. Data monitoring committees (DMCs) and confirmatory, adaptive clinical trials: the DMC charter.

- **Michael Krams, Johnson&Johnson**
Outline

• Categories of adaptive design
• Learning versus confirming
• Case study 1: ASTIN
• Case study 2: EuroHyp
• Case study 3: CDC
• Summary
Trials may adapt on…

- Allocation rule
- Sample size of next stage
- Stopping rules
  - Efficacy
  - Safety
  - Futility
- Recent developments
  - Compound
  - Indication
  - Endpoint
  - Patient population
Types of adaptive design

- First in human / dose escalation
  - Continual reassessment method (CRM)
    O’Quigley, 1990
- Multiple ascending dose / proof of concept
- Proof of concept / dose ranging
- Response adaptive dose ranging
- Seamless phase II / III with treatment selection
- Confirmatory phase III
Learning versus confirming

- Learn phase I; confirm phase IIA
- Learn phase IIB; confirm phase III
- Regulators prefer adaptive designs to be used during learning phase
- Encourage further exploration of their suitability in confirmatory trials

Case studies

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Case study 1

Summary


- Double-blind, placebo-controlled, Bayesian response adaptive dose-finding study
- Placebo and 15 doses (single 15 min i.v. infusion)
  - Doses 10, 16, 22, 27, 33, 38, 45, 52, 59, 67, 76, 84, 96, 108, 120mg
- Primary endpoint: Δ Scandinavian Stroke Scale (SSS) baseline to day 90
Case study 1
Summary


- **Real-time learning about dose-response**
  - Modelled via Normal Dynamic Linear Model
  - Early outcomes entered into longitudinal model to give predicted 90-day response
  - Identified optimal dose to be given to next patient

- **Adaptive treatment allocation**
  - Placebo 15% throughout trial
  - Optimal dose

- **Dynamic stopping rules**
  - Futility and efficacy
Case study 1

Results


• 966 patients randomised and treated

• 93% confirmed ischaemic stroke
  • Mean baseline severity SSS=28
  • Comparable demographics across treatment arms
  • Mean onset-to-treatment time 4hrs 08 mins
  • Mean door-to-needle time 2hrs 27 mins

• Stopped for futility (posterior probability 0.89)
Case study 1
A, Dose-effect curve of evaluable population on ΔSSS effect over placebo, with 95% CrI

Case study 1
Posterior probability in eligible patients of treatment being ineffective at ED95 (A) and treatment showing an effect of >2 points at ED95 (B)

Case study 1
Implementation


• Data monitoring committee
  • 3 clinicians, 1 statistician
  • Futility: $\Delta SSS < 1$ point, $ED_{95}$ versus placebo
  • Efficacy: $\Delta SSS > 2$ points, $ED_{95}$ versus placebo
  • Weekly updates of posterior probabilities of futility and efficacy – stop if either $>0.9$

• DMC independence and expertise key
  • Detailed charter critical
  • Accommodate unplanned analysis requests from DMC
Case study 1
Implementation


- Lengthy pre-trial preparation (18 months)
  - Upfront investment requiring commitment from whole research organisation
  - Substantial effort in creating and validating bespoke software

- Simulation complexity
  - Determine “type I / II errors” (although Bayesian)
  - Frequency of correct dose selection
  - Longitudinal model
  - Comparison with standard designs
Case study 1
Implementation


• Production/administration of multiple doses while protecting blind

• Longitudinal model: timely information for real-time analysis, adaptation and decision-making

• Speed of recruitment

• Documentation of all processes/actions for regulatory purposes
  • Engaged in early and ongoing discussions with regulators to avoid regulatory concerns
Case study 2
Summary

- EuroHyp – response adaptive dose ranging
- Hypothermia treatment for acute ischaemic stroke
  - i.v. infusion of chilled saline followed by **surface cooling** or **endovascular cooling** according to physician preference
Case study 2
Surface cooling
Case study 2
Summary

- EuroHyp – response adaptive dose ranging
- How low to reduce temperature?
  - 34 or 35 °C
- For how long?
  - 12 or 24hrs
- 2-D adaptive dose response scenario
Case study 2
Implementation

• No useful surrogate exists to drive adaptations
  • Objective endpoints key
• Instead use tolerability
  • As medical aids assist tolerability, less incentive to evaluate target temperature - instead aim for target temperature range and to maximise tolerability
• With tolerability aids in place would have limited power to identify differences between durations
• Pragmatic choice of feasible design covering entire 24hrs ‘at risk’ period
  • Considering adaptive design may improve research plan even if not ultimately adopted
Case study 3
Summary

• Chronic degenerative condition
• No current efficacious treatment
• Adaptive seamless phase II / III
  • Combine phase II, III results by combination test
• Phase II: 3 candidate treatments plus placebo
  • Retain fewer treatments in phase III
• Any treatment benefit anticipated to emerge over several years
Case study 3
Implementation

- Long period of action – cannot use target disability outcome measure at interim
  - Endpoints used at both stages must be well understood/accepted
  - Objective endpoints key
  - Cannot use seamless design to determine phase III outcome measure
- No need to compromise blinding going in to stage 2 of seamless design
Case study 3
Implementation

- No current established treatment
  - No known surrogate outcome for disability
  - Use lesser threshold of a “biologically plausible” endpoint: absence of effect indicates treatment not having anticipated mechanism of action
  - Adapt on biologically plausible biomarker at interim
- Substantial pre-trial simulation work
  - Operational characteristics
  - Feasible number of treatment arms in each phase
  - Validity of adapting on “biologically plausible” outcome
Adaptive design implementation
Summary

• Greater complexity
  • additional advance planning (3+ months)
• Secure/efficient information flow
  • real-time data analysis, communication, decision-making
• Objective endpoints
• Keep trial in context
  • issues/assumptions log
• Making case for funding
  • based on pre-trial simulations
• Independence and expertise of DMC
Other issues

- Technical/logistical challenges of randomisation/drug supply management
  - Solutions supporting adaptive design benefit all other trial implementations

- Information value rather than standard milestones
  - Compare versus standard design for key decision, e.g. ratio of time/patients needed

- Simulations should apply best-guess, optimistic, pessimistic scenarios and extreme cases to stress-test design
  - Gallo et al. Statistics in Biopharmaceutical Research 2010;2:513-521 presents case study where extreme case simulation would have helped
Other issues

- Protocol requirements
  - Justify adaptive design non-technically
  - Clarify DMC role and type I error control
  - List sensitivity analysis for operational bias: time trends in baseline characteristics, treatment efficacy
  - Simulation report provides design justification

- Funding applications
  - Driven by evidence from pre-trial simulations
  - Learning study: request mid-range
  - Confirmatory:
    » request upper end of range
    » further funding request informs on interim analysis findings and partially unblinds
Learning

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Confirming

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