Adaptive Trial Designs

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

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Adaptive trial designs

- "The wise **adapt** themselves to circumstances, as water moulds itself to the pitcher."

  Chinese proverb

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Acknowledgements

- Key references

Krams M *et al*. Adaptive approaches in clinical drug development: opportunities and challenges in design and implementation. *Pharm Med* 2003;23:139-148.

Fardipour P *et al*. Planning and executing response-adaptive learn-phase clinical trials: 1. The process. *Drug Information Journal* 2009;43:713-723.

Gaydos B *et al*. Good practices for adaptive clinical trials in pharmaceutical product development. *Drug Information Journal* 2009;43:539-556.

Quinlan J *et al*. Barriers and opportunities for implementation of adaptive designs in pharmaceutical product development. *Clinical Trials* 2010;7:167-173.

Gallo P *et al*. Data monitoring in adaptive dose-ranging trials. *Statistics in Biopharmaceutical Research* 2010;2:513-521.

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

- Michael Krams, Johnson&Johnson

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Outline

- Categories of adaptive design
- Learning versus confirming
- Case study 1: ASTIN
- Case study 2: EuroHyp
- Case study 3: CDC
- Summary

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Trials may adapt on…

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

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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

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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

- Sheiner LB, *Clin Pharmacol Ther* 1997;61:275-291
- Food and Drug Administration (2010), Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics (Draft Guidance). Silver Spring, MD: U.S. Food and Drug Administration. Available online at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf

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Case studies

- First in human / dose escalation
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- 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

Case studies

- 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 → 1 & 2
- Seamless phase II / III with treatment selection → 3
- Confirmatory phase III

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Case study 1
Summary

- Krams M et al. Acute stroke therapy by inhibition of neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke* 2003;34:2543-2548.

- 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

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Case study 1
Summary

- Krams M et al. Acute stroke therapy by inhibition of neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke* 2003;34:2543-2548.

- 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

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Case study 1
Results

- Krams M et al. Acute stroke therapy by inhibition of neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke* 2003;34:2543-2548.

- 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)

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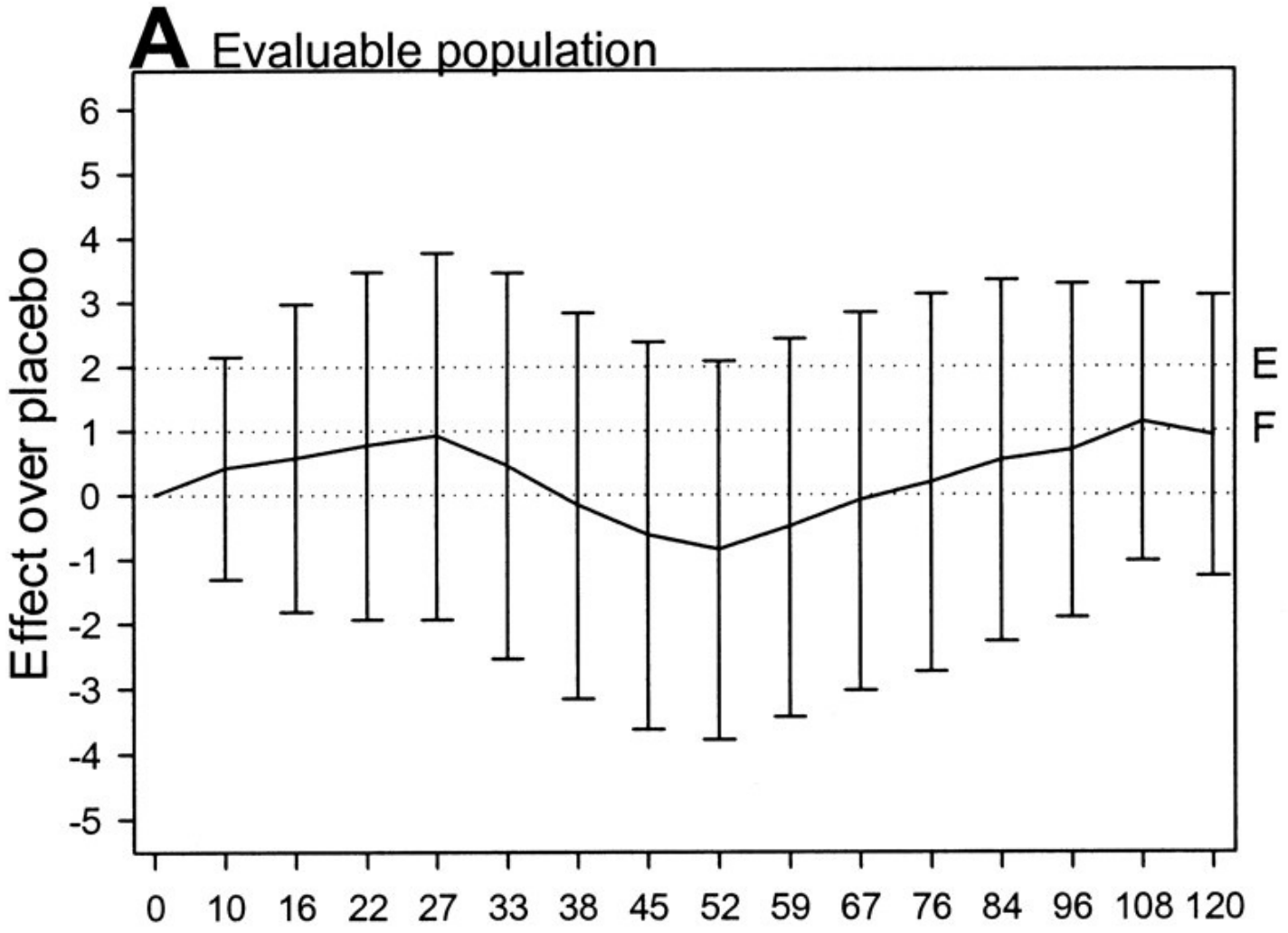
Case study 1

A, Dose-effect curve of evaluable population on ΔSSS effect over placebo, with 95% CrI

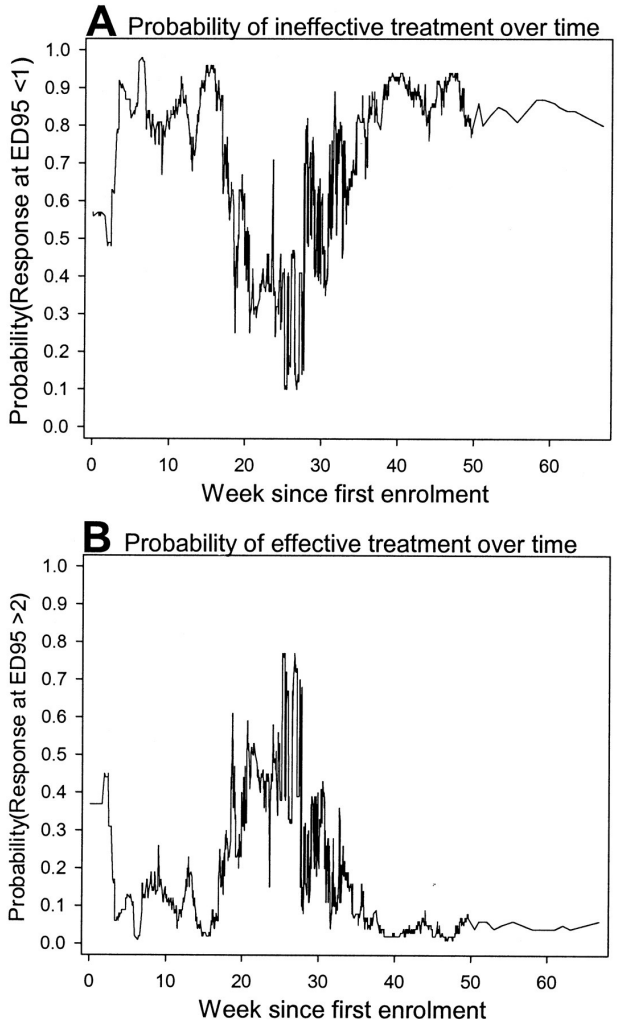


Krams, M. et al. Stroke 2003;34:2543-2548

Stroke

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)



Krams, M. et al. Stroke 2003;34:2543-2548

Stroke

Case study 1
Implementation

- Krams M et al. Acute stroke therapy by inhibition of neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke* 2003;34:2543-2548.

- Data monitoring committee
  - 3 clinicians, 1 statistician
  - Futility: ΔSSS <1 point, ED_{95} versus placebo
  - Efficacy: ΔSSS >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

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Case study 1
Implementation

- Krams M et al. Acute stroke therapy by inhibition of neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke* 2003;34:2543-2548.

- 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

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Case study 1
Implementation

- Krams M et al. Acute stroke therapy by inhibition of neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke* 2003;34:2543-2548.

- 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

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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

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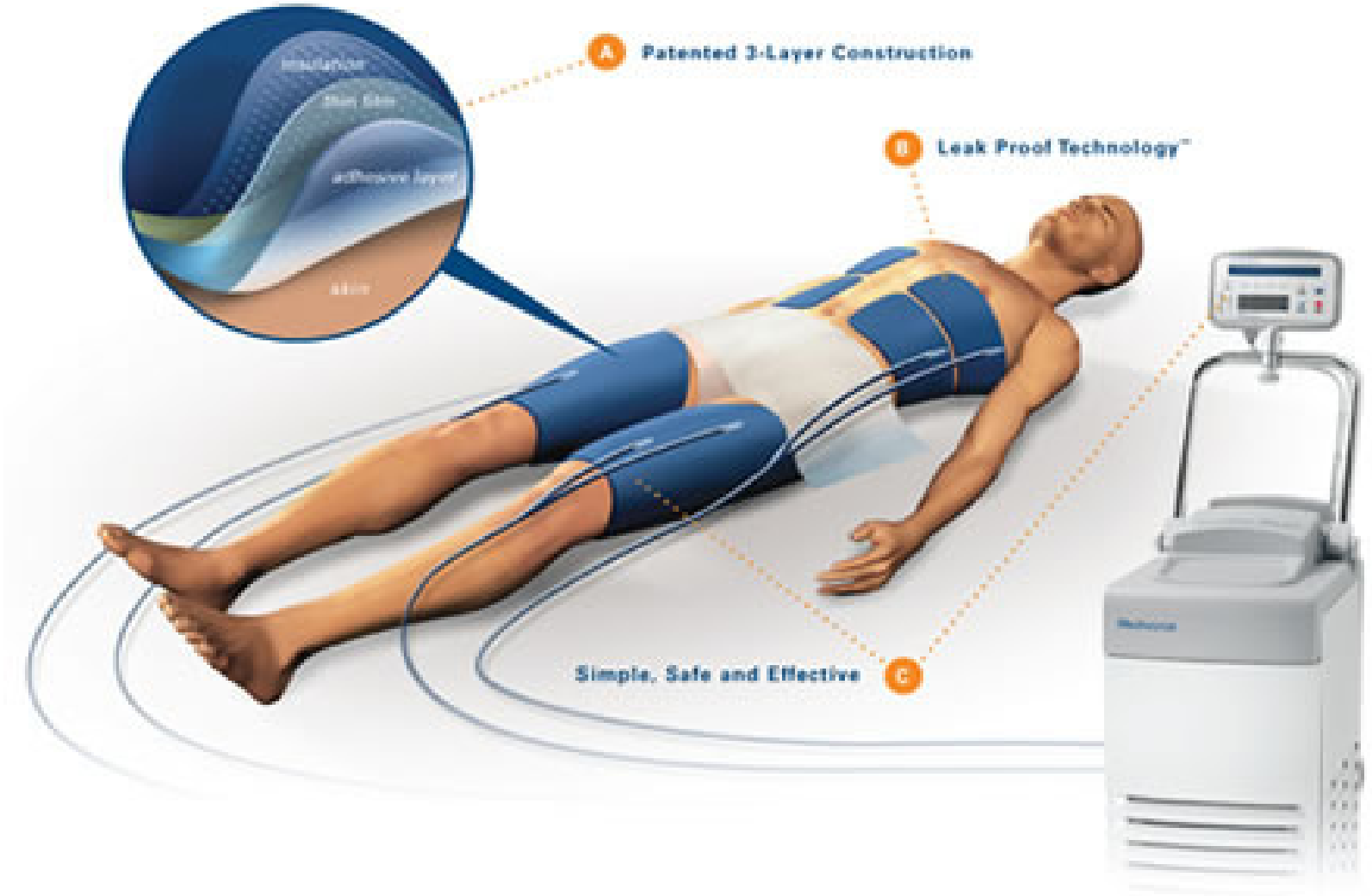
Case study 2
Surface cooling



Case study 2
Summary

- EuroHyp – response adaptive dose ranging
- How low to reduce temperature?
    - 34 or 35 ℃
- For how long?
    - 12 or 24hrs
- 2-D adaptive dose response scenario
    - Yin G, Yuan Y. A latent contingency table approach to dose finding for combinations of two agents. *Biometrics* 2009;65:866-875.

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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

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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

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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

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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

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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

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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

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Learning

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Confirming

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