Adaptive design development and implementation: practical experiences from the DexFEM trial

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Adaptive Designs Workshop
Background

Packing the suitcase
  • Design development, pre-trial simulations

Having a route map
  • Trial plans and procedures

Are we there yet?
  • Experiences so far and the road ahead
Menstrual bleeding complaints affect quality of life and have a substantial societal burden – major impact on health care resource use.

Current medical therapy for heavy menstrual bleeding (HMB) is often ineffective or associated with unacceptable side effects.

Unmet clinical need for targeted, effective, medical treatment for HMB.

Experimental studies have identified enhanced endometrial inactivation of cortisol as a possible mechanism for HMB.

"Rescue" of endometrial glucocorticoid deficiency would provide a novel approach to therapy for HMB.

Dexamethasone - a glucocorticoid receptor agonist - a potential treatment.
BACKGROUND: THE DexFEM PROGRAMME

DexFEM: Dexamethasone For Excessive Menstruation
(MRC funded, ref MR/J003611/1)

- Aims to determine if taking Dex orally reduces menstrual blood loss
- Two workup studies allow investigation of mechanistic aspects, piloting of trial procedures
- Main study: 100 women randomised to either placebo or an active dose
- Potential range of doses to be considered in the range 0.4mg to 1.8mg/day

- Two objectives
  - Identify optimal dose – ED95 – lowest dose with near (95% of) maximal efficacy
  - Show superiority of Dex over Placebo at optimal dose

- Response adaptive design proposed
• **Primary outcome:**

  change in menstrual blood loss (MBL)  
  from baseline (average of 2 screening MBLs)  
  to outcome (average MBL in menstrual cycles 2&3 of treatment)

• **Inclusion:** MBL greater than 50mL per cycle
Bayesian normal dynamic linear model (NDLM - West & Harrison 1997) to (1) estimate relationship of dexamethasone dose with primary outcome and (2) guide adaptations

**BACKGROUND:**

**Key Features:**

- Bayesian normal dynamic linear model (NDLM - West & Harrison 1997) to (1) estimate relationship of dexamethasone dose with primary outcome and (2) guide adaptations
Design options

- How many adaptations? Spacing?
- What rules should adaptation be based upon?
- How many doses to study?

Scenarios

Require a design which would perform well under a variety of scenarios

Software

- SAS to simulate hypothetical DexFEM trial data
- WinBUGS for model estimation
<table>
<thead>
<tr>
<th>Number of adaptations</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>5</th>
</tr>
</thead>
</table>
Timing of adaptations: early in trial, evenly spread, late in trial.
Adaptation rule

1. Proportionate to current probability that each dose affects at least some reduction in MBL versus placebo

2. For each dose, reduction in variance of estimate of response at ED95 from its posterior predictive distribution after one future patient is studied on that dose – “one step ahead” approach. Importance sampling (Gelfand et al, 1996) used to assist computational feasibility.
<table>
<thead>
<tr>
<th>Number of doses studied</th>
<th>4 active plus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 active plus placebo</td>
</tr>
</tbody>
</table>
Proportion allocated to placebo throughout trial

1/7 (14%)
2/7 (28%)
PRE-TRIAL SIMULATIONS: SCENARIOS

Dose-response curve shapes:
steep ascent, shallow ascent, non-monotone, flat
Mean MBL treatment effect at best dose

16 mL

8 mL
Within patient MBL residual standard deviation

18 mL
22 mL
26 mL
Treatment interaction with baseline MBL

No interaction
20% of baseline MBL at most effective dose
Heteroscedasticity

No heteroscedasticity
Variance changes linearly with exponential of mean MBL
Recruitment rate

2 patients per month
4 patients per month
PRE-TRIAL SIMULATIONS

- Fully factorial investigation to characterise all design options / scenarios – would require nearly 12,000 combinations

- A core set of scenarios and design options were studied in a fully factorial manner

- Other scenarios and design options were studied in a fractional factorial

- In total, 150 combinations of scenarios and design options are examined

- Each combination simulated 200 times

- Total processing time approximately two months
Properties of Interest

- Does adaptation develop as expected?
- Type I error
- Statistical power (at least one dexamethasone dose correctly identified as being efficacious)

Estimated effect on power/type I error of each design option / scenario via normal linear modelling of the fractional factorial design
SIMULATION RESULTS: ADAPTATION

3 adaptations after 20, 45, 70 randomisations
Most effective dose between 1.0mg and 1.2mg

Average over 200 simulated trials
SIMULATION RESULTS: TYPE I ERROR

[Bar chart showing type I error rates for different variance scenarios, heteroscedasticity presence, and treatment interaction conditions.]

- Variance scenario: 17.9^2
- Variance scenario: 22.0^2
- Variance scenario: 26.0^2
- Heteroscedasticity absent
- Heteroscedasticity present
- Treatment interaction
- No treatment interaction
SIMULATION RESULTS: TYPE I ERROR
Overall: Type I error 6.2% (95% CI, 5.5% to 6.9%)
SIMULATION RESULTS: POWER

![Power Increase Diagram]

- The diagram shows the power increase for different adaptation schedules.
- The x-axis represents the adaptation schedule, while the y-axis shows the power increase.
- Each point on the graph represents the power increase for a specific adaptation schedule, with error bars indicating variability.
- The graph highlights a significant power increase for a certain adaptation schedule, circled for emphasis.

**Key Points:**
- **Power Increase:** Measured in a specific units.
- **Adaptation Schedule:** Specifies the intervals at which the adaptation occurs.
- **Error Bars:** Indicate the range of variability for each point.
SIMULATION RESULTS: POWER

- Adaptation rule #2
- Adaptation rule #1
- Four active closes
- Six active closes
- 2/7 allocated to placebo
- 1/7 allocated to placebo

Power increase
## Simulation Results: Power

<table>
<thead>
<tr>
<th>Design effect</th>
<th>Levels</th>
<th>Mean power change versus reference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum mean effect of dexamethasone</td>
<td>16 mL</td>
<td>+44%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>8 mL</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>18 mL</td>
<td>+17%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>22 mL</td>
<td>+8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>26 mL</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Curve</td>
<td>(1) Sine curve: steep</td>
<td>-9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>(2) Sine curve: slow</td>
<td>-5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>(3) Non-monotone</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Interaction</td>
<td>No interaction</td>
<td>+3%</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Treatment x baseline MBL interaction</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Randomisation rate</td>
<td>2 pts / month</td>
<td>-0.7%</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>4 pts / month</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Heteroscedasticity</td>
<td>Absent</td>
<td>+0.4%</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Reference</td>
<td>-</td>
</tr>
</tbody>
</table>
Simulation Results: Summary

A robust adaptive design for a randomised, double-blind, placebo controlled trial to identify the minimum dexamethasone dose with near-maximal efficacy:

- 5 adaptations, evenly spaced after 16, 32, 50, 66, 84 randomisations

- Adaptation rule based on precision (reciprocal of variance) of estimated response at the ED95 (the minimum dose with near-maximal efficacy) after one further patient has been randomised (one-step-ahead approach)

- 6 dexamethasone doses (0.4, 0.8, 1.0, 1.2, 1.5, 1.8mg total daily dose)

- (2/7) of patients allocated to placebo throughout
Statistical power 93.8% (95% confidence interval 91.9% to 95.8%)
- maximum mean benefit over placebo of 16 mL
- within patient MBL standard deviation of 18 mL
- randomising 4 patients per month
- averaged across: all shapes of dose response curve
  - heteroscedasticity (present/absent)
  - interaction with baseline MBL (present/absent)
HAVING A ROUTE MAP: TRIAL PLANS AND PROCEDURES

**Timeline**

**Event**

**Communication**

**Pre-trial**

- Randomisation takes place which brings recruitment to an adaptation point

**During trial**

- Lead statistician runs adaptation analysis using snapshot and produces report
- Lead statistician stores snapshot of data view centrally

**2-3 working days**

- Second statistician validates analysis

**1 working day**

- Proposed probabilities and report forwarded to DMC
- DMC approval received
- Lead statistician alerts IT of new allocation probabilities (to 3dp)

**Response within 7 days**

- Inform DMC, TSC, trial coordinator

**1 working day**

- IT updates randomisation probabilities, statistician verifies, plus automatic check probabilities sum to 1
- Inform DMC, TSC, trial coordinator
- Updated allocation goes live immediately

- Inform pharmacy to allow planning of drug supply
Not yet!

- Clarification of adaptive design scope
- Communication is key
- Multidisciplinary nature
- Independent expert oversight from DMC
  - The trial independent Data Monitoring Committee (DMC) commented on the plan for the pre-trial simulations
  - During the trial, the DMC will review evidence from the interim analyses and approve the proposed updates to the randomisation probabilities
- 12 month milestone passed
- First patient to be recruited March 2014
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REFERENCES


http://www.tonyohagan.co.uk/shelf/


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