Adaptive Designs for Dose Escalation Studies
- A Simulation Study -

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Background

Traditional Escalation Rule - 3+3-Design

Parametric Approach - Modified 3+3-Design

The Simulation Study - Results
Dose Escalation Studies

- Phase I studies / first in humans
Dose Escalation Studies

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- Small scale, estimation purpose, learn about the dose-response-relationship
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- Primary interest: safety, not efficacy
Dose Escalation Studies

- Phase I studies / first in humans
- Small scale, estimation purpose, learn about the dose-response-relationship
- Primary interest: safety, not efficacy
- Specific goal: find maximum tolerated dose (MTD)
Typical Dose-Response-Curves and Therapeutic Window

Dose-Response-Curves

- efficacy
- toxicity
- lower bound of therap. window
- upper bound of therap. window

minED, MTD

Dose

probability
Problems and Challenges

- Little / no experience with the drug in humans
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- Little / no prior knowledge (e.g. about model and parameters)
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- Ethical concerns:
  - Do not treat probands / patients at highly toxic doses
  - Do not treat patients at ineffective doses
  - Use as few probands / patients as necessary
Problems and Challenges

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- Little / no prior knowledge (e.g. about model and parameters)
- Ethical concerns:
  - Do not treat probands / patients at highly toxic doses
  - Do not treat patients at ineffective doses
  - Use as few probands / patients as necessary
- and still: get reliable results
3+3-Design

- Define a sequence of doses (usually: modified Fibonacci sequence)
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- Treat cohorts of 3 patients, start with the lowest dose
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- De-escalate if the dose is 'toxic'
3+3-Design

- Define a sequence of doses (usually: modified Fibonacci sequence)
- Treat cohorts of 3 patients, start with the lowest dose
- Escalate if the dose is 'safe'
- De-escalate if the dose is 'toxic'
- Treat more patients at the same dose if the results are indecisive
Underlying Assumptions

- MTD = maximal dose with probability of toxicity < $\frac{1}{3}$
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- MTD = maximal dose with probability of toxicity $< \frac{1}{3}$
- Binary toxicity outcome (dose limiting toxicity or no DLT)
Underlying Assumptions

- MTD $=$ maximal dose with probability of toxicity $< \frac{1}{3}$
- Binary toxicity outcome (dose limiting toxicity or no DLT)
- No parametric model
Underlying Assumptions

- MTD = maximal dose with probability of toxicity $< \frac{1}{3}$
- Binary toxicity outcome (dose limiting toxicity or no DLT)
- No parametric model
- Probability of toxicity is monotonously increasing with dose
Flowchart: 3+3-Design

START

dose step=0

dose escalation:
dose step=dose step+1

Inclusion 1:
patient 1,2,3

0

number of DLTs

> 0

number of patients treated
at dose step+1

< 0

= 0

MTD = dose step

STOP

Inclusion 2:
patient 4,5,6

0

number of DLTs

> 0

= 0

dose reduction:
dose step=dose step-1

3

number of patients in
dose step

6

< 1

total number of DLTs

> 1

< 1

total number of DLTs

< 1

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Adaptive Designs for Dose Escalation Studies
Study example: 3+3-Design

![Graph showing dose escalation and patients valid for dose escalation decision]
Properties of the 3+3 Designs

- Small number of DLTs

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Adaptive Designs for Dose Escalation Studies
Properties of the 3+3 Designs

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- Number of patients gets large when MTD is 'far away' from starting dose
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- Under-estimation much more likely
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- Over-estimation unlikely
- Under-estimation much more likely

⇒ conservative (safe) and easy to use in practice
Other Recently Proposed Models and Designs

- Bayesian approaches (e.g. CRM)
- Parametric and nonparametric methods
- Binary, categorical and continuous outcomes
- Univariate and bivariate outcomes
Other Recently Proposed Models and Designs

- Bayesian approaches (e.g. CRM)
- Parametric and nonparametric methods
- Binary, categorical and continuous outcomes
- Univariate and bivariate outcomes
- here: compare the 3+3-Design with a Bayesian and an adaptive parametric approach
General Idea

- Select a model appropriate for the dose-response-relationship (e.g. logistic, proportional odds)
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- Use 3+3-Design until parameter estimation is possible in the selected model
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- Construct conditional locally optimal design for these parameter estimates
- Treat next cohort of patients according to this design
General Idea

- Select a model appropriate for the dose-response-relationship (e.g. logistic, proportional odds)
- Use 3+3-Design until parameter estimation is possible in the selected model
- Construct conditional locally optimal design for these parameter estimates
- Treat next cohort of patients according to this design
- Repeat estimation after each cohort and adjust design
Flowchart: Modified 3+3-Design

START

3+3-Design (3 patients per step)

stop criterion for the 3+3-Design met?

MLE exists?

estimate parameters and find new optimal design

include next patient(s)

maximum sample size reached?

STOP

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Conditional Locally Optimal Design

- maximize the overall information of the experiment when allocating \( n \) additional subjects to doses within the design region, treating the design points used so far as forced measurements
Conditional Locally Optimal Design

- maximize the overall information of the experiment when allocating $n$ additional subjects to doses within the design region, treating the design points used so far as forced measurements
- denote
  - design points used so far: $x_{obs}$
  - estimated parameters for the model: $\hat{\theta}$
  - information matrix for design point(s) $x$ and parameters $\theta$: $M(x, \theta)$
  - design region $X$
maximize the overall information of the experiment when allocating $n$ additional subjects to doses within the design region, treating the design points used so far as forced measurements

denote

- design points used so far: $x_{obs}$
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- information matrix for design point(s) $x$ and parameters $\theta$: $M(x, \theta)$
- design region $X$

then: conditional information matrix

$$M_c = M(x_{obs}, \hat{\theta}) + \sum_{i=1}^{n} M(x_i, \hat{\theta}), \quad x_i \in X$$
Conditional Locally Optimal Design

- maximize the overall information of the experiment when allocating $n$ additional subjects to doses within the design region, treating the design points used so far as forced measurements
- denote
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  - design region $X$
- then: conditional information matrix
  $$M_c = M(x_{obs}, \hat{\theta}) + \sum_{i=1}^{n} M(x_i, \hat{\theta}), \quad x_i \in X$$
- maximize function of $M_c$ according to optimality criterion
Parameters to be specified

- Sequence of doses (same as for 3+3-Design)
Parameters to be specified

- Sequence of doses (same as for 3+3-Design)
- Maximum sample size (as stopping rule)
Parameters to be specified

- Sequence of doses (same as for 3+3-Design)
- Maximum sample size (as stopping rule)
- Optimality criterion
Parameters to be specified

- Sequence of doses (same as for 3+3-Design)
- Maximum sample size (as stopping rule)
- Optimality criterion
- Cohort size
Parameters to be specified

- Sequence of doses (same as for 3+3-Design)
- Maximum sample size (as stopping rule)
- Optimality criterion
- Cohort size
- Lower and upper limits for design space
Dose-Response-Scenarios

Different Dose–Response–Scenarios

- Scenario 1
- Scenario 2
- Scenario 3
- Scenario 4
- Scenario 5
- Scenario 6

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Adaptive Designs for Dose Escalation Studies
Dose-Response-Scenarios

- Scenario 1: based on logistic regression model fit to real data, 
  $\mu = 30, \sigma = 7.67 \Rightarrow \text{MTD} = 24.7 \text{ mg}$
Dose-Response-Scenarios

- Scenario 1: based on logistic regression model fit to real data, \( \mu = 30, \sigma = 7.67 \) \( \Rightarrow \) MTD = 24.7 mg
- Scenario 2: based on a 4-category proportional odds model fit to real data, \( \mu = 23.8, \sigma = 8.3 \) \( \Rightarrow \) MTD = 18 mg
Dose-Response-Scenarios

- Scenario 1: based on logistic regression model fit to real data, $\mu = 30, \sigma = 7.67 \Rightarrow MTD=24.7 \text{ mg}$
- Scenario 2: based on a 4-category proportional odds model fit to real data, $\mu = 23.8, \sigma = 8.3 \Rightarrow MTD=18 \text{ mg}$
- Scenario 3: 'safe' scenario, $\mu=50, \sigma=14.43 \Rightarrow MTD=40 \text{ mg}$
- Scenario 4: 'toxic' scenario, $\mu=11, \sigma=4.33 \Rightarrow MTD=8 \text{ mg}$
- Scenario 5: $E_{\text{max}}$-Model with $ED_{50}=50, N=0.7 \Rightarrow MTD=18.6 \text{ mg}$
- Scenario 6: $E_{\text{max}}$-Model with $ED_{50}=28, N=1.6 \Rightarrow MTD=18.2 \text{ mg}$
Dose-Response-Scenarios

- Scenario 1: based on logistic regression model fit to real data, $\mu = 30, \sigma = 7.67 \Rightarrow MTD=24.7$ mg
- Scenario 2: based on a 4-category proportional odds model fit to real data, $\mu = 23.8, \sigma = 8.3 \Rightarrow MTD=18$ mg
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Dose-Response-Scenarios

- Scenario 1: based on logistic regression model fit to real data, \( \mu = 30, \sigma = 7.67 \Rightarrow MTD=24.7 \text{ mg} \)
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Dose-Response-Scenarios

- Scenario 1: based on logistic regression model fit to real data, $\mu = 30, \sigma = 7.67 \Rightarrow \text{MTD}=24.7 \text{ mg}$
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- Scenario 4: 'toxic' scenario, $\mu = 11, \sigma = 4.33 \Rightarrow \text{MTD}=8 \text{ mg}$
- Scenario 5: $E_{max}$-Model with ED50=50, N=0.7 ; $\Rightarrow \text{MTD}=18.6 \text{ mg}$
- Scenario 6: $E_{max}$-Model with ED50=28, N=1.6 ; $\Rightarrow \text{MTD}=18.2 \text{ mg}$
Models and Parameter Specifications

▶ used doses (mg): 0.6, 1.2, 2, 3, 4, 5.3, 7, 9, 12.4, 16.53, 22, 29.4
Models and Parameter Specifications

- used doses (mg): 0.6, 1.2, 2, 3, 4, 5.3, 7, 9, 12.4, 16.53, 22, 29.4
- 100,000 simulation runs
Models and Parameter Specifications

- used doses (mg): 0.6, 1.2, 2, 3, 4, 5.3, 7, 9, 12.4, 16.53, 22, 29.4
- 100 000 simulation runs
- underlying model: logistic (both for Bayesian and parametric approach)
Models and Parameter Specifications - Bayesian ADEPT

- a-priori-information: $TD_{20} = 0.6 \text{ mg}$, $TD_{50} = 29.4 \text{ mg}$, amount of prior information equivalent to one observation each
Models and Parameter Specifications - Bayesian ADEPT

- a-priori-information: $TD20 = 0.6 \text{ mg}$, $TD50 = 29.4 \text{ mg}$, amount of prior information equivalent to one observation each
- gain functions:
  - variance gain function
  - patient gain function
Models and Parameter Specifications - Bayesian ADEPT

- a-priori-information: TD20 = 0.6 mg, TD50 = 29.4 mg, amount of prior information equivalent to one observation each
- gain functions:
  - variance gain function
  - patient gain function
- cohort size: 1, 2 (3)
Models and Parameter Specifications - Bayesian ADEPT

- a-priori-information: TD20 = 0.6 mg, TD50 = 29.4 mg, amount of prior information equivalent to one observation each
- gain functions:
  - variance gain function
  - patient gain function
- cohort size: 1, 2 (3)
- stopping criterion: \( \frac{\text{upper limit of 95\% credibility interval}}{\text{lower limit of 95\% credibility interval}} < 5 \)
  or sample size = 60
Models and Parameter Specifications - Parametric Approach

- optimality criterion: D, c (MTD is a linear function of the parameters)
Models and Parameter Specifications - Parametric Approach

- optimality criterion: D, c (MTD is a linear function of the parameters)
- cohort size: 1 (2)
Optimality criterion: D, c (MTD is a linear function of the parameters)

- Cohort size: 1 (2)
- Lower bound for design space: 0
Models and Parameter Specifications - Parametric Approach

- optimality criterion: $D, c$ (MTD is a linear function of the parameters)
- cohort size: 1 (2)
- lower bound for design space: 0
- upper bound for design space:
  - dose level above maximum dose level used so far
  - dose level above current $\hat{MTD}$
  - never larger than maximum prespecified dose level
Models and Parameter Specifications - Parametric Approach

- optimality criterion: $D, c$ (MTD is a linear function of the parameters)
- cohort size: 1 (2)
- lower bound for design space: 0
- upper bound for design space:
  - dose level above maximum dose level used so far
  - dose level above current $\hat{MTD}$
  - never larger than maximum prespecified dose level
- maximum sample size $=$ median sample size from 3+3-Design
### Results - Scenario 1

**Recommendation as MTD in %**

<table>
<thead>
<tr>
<th>Dose</th>
<th>≤ 12.4 mg</th>
<th>16.53 mg</th>
<th>22 mg</th>
<th>29.4 mg</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3+3-Design</strong></td>
<td>33.84</td>
<td>27.14</td>
<td>33.08</td>
<td>5.43</td>
<td>0.52</td>
</tr>
<tr>
<td>ADEPT(var,coh=2)</td>
<td>8.61</td>
<td>38.74</td>
<td>45.95</td>
<td>6.69</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=2)</td>
<td>3.21</td>
<td>22.60</td>
<td>57.66</td>
<td>16.53</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(var,coh=1)</td>
<td>8.44</td>
<td>40.31</td>
<td>45.64</td>
<td>5.62</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=1)</td>
<td>5.54</td>
<td>19.94</td>
<td>64.18</td>
<td>13.34</td>
<td>0</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=1)</td>
<td>21.95</td>
<td>24.37</td>
<td>41.75</td>
<td>11.43</td>
<td>0.50</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=2)</td>
<td>23.30</td>
<td>29.99</td>
<td>34.62</td>
<td>11.59</td>
<td>0.50</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=1)</td>
<td>21.99</td>
<td>26.90</td>
<td>39.27</td>
<td>11.33</td>
<td>0.50</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=2)</td>
<td>22.68</td>
<td>29.89</td>
<td>35.48</td>
<td>11.45</td>
<td>0.50</td>
</tr>
</tbody>
</table>
### Results - Scenario 1 (cont.)

<table>
<thead>
<tr>
<th></th>
<th>sample size (mean)</th>
<th>DLTs (mean)</th>
<th>patients treated above MTD (mean)</th>
<th>MSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3-Design</td>
<td>37.55</td>
<td><strong>3.12</strong></td>
<td><strong>1.16</strong></td>
<td>71.08</td>
</tr>
<tr>
<td>ADEPT(var,coh=2)</td>
<td>29.84</td>
<td>8.48</td>
<td>14.71</td>
<td>25.20</td>
</tr>
<tr>
<td>ADEPT(pat,coh=2)</td>
<td>33.71</td>
<td>9.80</td>
<td>14.01</td>
<td>19.84</td>
</tr>
<tr>
<td>ADEPT(var,coh=1)</td>
<td><strong>28.29</strong></td>
<td>8.06</td>
<td>14.16</td>
<td>25.22</td>
</tr>
<tr>
<td>ADEPT(pat,coh=1)</td>
<td>34.09</td>
<td>10.20</td>
<td>13.87</td>
<td><strong>15.89</strong></td>
</tr>
<tr>
<td>mod.3+3 (D,ul=1)</td>
<td>37.07</td>
<td>4.27</td>
<td>4.81</td>
<td>60.40</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=2)</td>
<td>37.07</td>
<td>4.24</td>
<td>4.01</td>
<td>57.85</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=1)</td>
<td>37.07</td>
<td>4.15</td>
<td>4.18</td>
<td>58.39</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=2)</td>
<td>37.07</td>
<td>4.31</td>
<td>4.05</td>
<td>56.70</td>
</tr>
</tbody>
</table>
## Recommendation as MTD in %

<table>
<thead>
<tr>
<th>Dose</th>
<th>≤ 9.3 mg</th>
<th>12.4 mg</th>
<th>16.53 mg</th>
<th>22 mg</th>
<th>29.4 mg</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3-Design</td>
<td>62.10</td>
<td>18.10</td>
<td>11.91</td>
<td>4.26</td>
<td>0.16</td>
<td>3.48</td>
</tr>
<tr>
<td>ADEPT(var,coh=2)</td>
<td>19.90</td>
<td>33.87</td>
<td>39.05</td>
<td>7.11</td>
<td>0.08</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=2)</td>
<td>9.01</td>
<td>22.83</td>
<td><strong>49.51</strong></td>
<td>17.72</td>
<td>0.94</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(var,coh=1)</td>
<td>17.64</td>
<td>34.40</td>
<td>40.55</td>
<td>7.40</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=1)</td>
<td>8.12</td>
<td>25.12</td>
<td>47.84</td>
<td>18.40</td>
<td>0.53</td>
<td>0</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=1)</td>
<td>35.32</td>
<td>24.32</td>
<td>25.78</td>
<td>8.44</td>
<td>2.83</td>
<td>3.31</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=2)</td>
<td>43.37</td>
<td>21.59</td>
<td>22.97</td>
<td>6.82</td>
<td>1.94</td>
<td>3.31</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=1)</td>
<td>34.35</td>
<td>25.69</td>
<td>25.62</td>
<td>8.22</td>
<td>2.82</td>
<td>3.31</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=2)</td>
<td>41.94</td>
<td>22.23</td>
<td>23.69</td>
<td>6.82</td>
<td>1.97</td>
<td>3.34</td>
</tr>
</tbody>
</table>
## Results - Scenario 2 (cont.)

<table>
<thead>
<tr>
<th></th>
<th>sample size (mean)</th>
<th>DLTs (mean)</th>
<th>patients treated above MTD (mean)</th>
<th>MSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3-Design</td>
<td>31.17</td>
<td>3.72</td>
<td>0.91</td>
<td>89.65</td>
</tr>
<tr>
<td>ADEPT(var,coh=2)</td>
<td>26.94</td>
<td>7.91</td>
<td>9.12</td>
<td>20.93</td>
</tr>
<tr>
<td>ADEPT(pat,coh=2)</td>
<td>30.43</td>
<td>8.70</td>
<td>8.50</td>
<td>16.72</td>
</tr>
<tr>
<td>ADEPT(var,coh=1)</td>
<td><strong>24.92</strong></td>
<td>7.37</td>
<td>7.78</td>
<td>19.27</td>
</tr>
<tr>
<td>ADEPT(pat,coh=1)</td>
<td>29.09</td>
<td>8.46</td>
<td>8.56</td>
<td><strong>15.84</strong></td>
</tr>
<tr>
<td>mod.3+3 (D,ul=1)</td>
<td>29.91</td>
<td>4.97</td>
<td>4.05</td>
<td>59.98</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=2)</td>
<td>29.91</td>
<td>4.51</td>
<td>3.04</td>
<td>60.48</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=1)</td>
<td>29.91</td>
<td>4.65</td>
<td>3.43</td>
<td>58.25</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=2)</td>
<td>29.91</td>
<td>4.61</td>
<td>3.15</td>
<td>59.17</td>
</tr>
</tbody>
</table>
## Results - Scenario 3

### Recommendation as MTD in %

<table>
<thead>
<tr>
<th>Dose</th>
<th>$\leq 16.53$ mg</th>
<th>22 mg</th>
<th>29.4 mg</th>
<th>NA</th>
</tr>
</thead>
<tbody>
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<td>3+3-Design</td>
<td>33.54</td>
<td>31.34</td>
<td>33.98</td>
<td>1.14</td>
</tr>
<tr>
<td>ADEPT(var,coh=2)</td>
<td>4.76</td>
<td>2.09</td>
<td><strong>93.15</strong></td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=2)</td>
<td>8.05</td>
<td>1.88</td>
<td>90.07</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(var,coh=1)</td>
<td>6.42</td>
<td>2.29</td>
<td>91.30</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=1)</td>
<td>12.11</td>
<td>1.89</td>
<td>86.00</td>
<td>0</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=1)</td>
<td>24.36</td>
<td>21.47</td>
<td>53.04</td>
<td>1.14</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=2)</td>
<td>23.28</td>
<td>16.99</td>
<td>58.59</td>
<td>1.14</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=1)</td>
<td>23.96</td>
<td>20.67</td>
<td>54.23</td>
<td>1.14</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=2)</td>
<td>22.59</td>
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<td>59.27</td>
<td>1.15</td>
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### Results - Scenario 3 (cont.)

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<th>Sample Size (mean)</th>
<th>DLTs (mean)</th>
<th>Patients Treated Above MTD (mean)</th>
<th>MSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3-Design</td>
<td>37.21</td>
<td>2.30</td>
<td>0</td>
<td>153.62</td>
</tr>
<tr>
<td>ADEPT(var, coh=2)</td>
<td>58.47</td>
<td>7.48</td>
<td>0</td>
<td>26.41</td>
</tr>
<tr>
<td>ADEPT(pat, coh=2)</td>
<td>58.56</td>
<td>10.26</td>
<td>0</td>
<td>53.41</td>
</tr>
<tr>
<td>ADEPT(var, coh=1)</td>
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<td>7.37</td>
<td>0</td>
<td>36.48</td>
</tr>
<tr>
<td>ADEPT(pat, coh=1)</td>
<td>58.96</td>
<td>10.62</td>
<td>0</td>
<td>87.13</td>
</tr>
<tr>
<td>mod.3+3 (D, ul=1)</td>
<td>36.61</td>
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<td>0</td>
<td>126.54</td>
</tr>
<tr>
<td>mod.3+3 (D, ul=2)</td>
<td>36.61</td>
<td>2.70</td>
<td>0</td>
<td>104.84</td>
</tr>
<tr>
<td>mod.3+3 (c, ul=1)</td>
<td>36.61</td>
<td>2.59</td>
<td>0</td>
<td>118.22</td>
</tr>
<tr>
<td>mod.3+3 (c, ul=2)</td>
<td>36.60</td>
<td>2.75</td>
<td>0</td>
<td>101.90</td>
</tr>
</tbody>
</table>
## Results - Scenario 4

### Recommendation as MTD in %

<table>
<thead>
<tr>
<th>Dose</th>
<th>( \leq 4 \text{ mg} )</th>
<th>5.3 mg</th>
<th>7 mg</th>
<th>9.3 mg</th>
<th>( \geq 12.4 \text{ mg} )</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3-Design</td>
<td>60.50</td>
<td>16.3</td>
<td>12.16</td>
<td>3.85</td>
<td>0.29</td>
<td>6.90</td>
</tr>
<tr>
<td>ADEPT(var,coh=2)</td>
<td>15.44</td>
<td>27.11</td>
<td>33.80</td>
<td>20.24</td>
<td>3.40</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=2)</td>
<td>6.97</td>
<td>17.69</td>
<td>37.17</td>
<td>29.97</td>
<td>8.22</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(var,coh=1)</td>
<td>14.41</td>
<td>26.45</td>
<td>33.37</td>
<td>20.46</td>
<td>5.31</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=1)</td>
<td>6.76</td>
<td>18.68</td>
<td><strong>38.64</strong></td>
<td>30.35</td>
<td>5.58</td>
<td>0</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=1)</td>
<td>35.60</td>
<td>21.03</td>
<td>22.53</td>
<td>10.47</td>
<td>3.81</td>
<td>6.67</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=2)</td>
<td>42.97</td>
<td>19.26</td>
<td>18.55</td>
<td>9.36</td>
<td>3.31</td>
<td>6.55</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=1)</td>
<td>35.88</td>
<td>22.14</td>
<td>21.13</td>
<td>10.08</td>
<td>4.22</td>
<td>6.55</td>
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<tr>
<td>mod.3+3 (c,ul=2)</td>
<td>42.43</td>
<td>19.95</td>
<td>18.19</td>
<td>9.62</td>
<td>3.17</td>
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### Results - Scenario 4 (cont.)

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<th></th>
<th>sample size (mean)</th>
<th>DLTs (mean)</th>
<th>patients treated above MTD (mean)</th>
<th>MSE</th>
</tr>
</thead>
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<tr>
<td>3+3-Design</td>
<td>22.70</td>
<td>3.52</td>
<td>1.13</td>
<td>15.10</td>
</tr>
<tr>
<td>ADEPT(var,coh=2)</td>
<td>24.05</td>
<td>7.57</td>
<td>6.84</td>
<td>4.88</td>
</tr>
<tr>
<td>ADEPT(pat,coh=2)</td>
<td>33.71</td>
<td>8.44</td>
<td>7.63</td>
<td>6.12</td>
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<tr>
<td>ADEPT(var,coh=1)</td>
<td>23.05</td>
<td>7.26</td>
<td>7.20</td>
<td>5.35</td>
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<td>ADEPT(pat,coh=1)</td>
<td>26.55</td>
<td>8.03</td>
<td>8.04</td>
<td>4.64</td>
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<td>mod.3+3 (D,ul=1)</td>
<td>21.38</td>
<td>4.03</td>
<td>2.57</td>
<td>10.84</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=2)</td>
<td>21.38</td>
<td>3.68</td>
<td>1.92</td>
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<td>21.38</td>
<td>3.70</td>
<td>2.04</td>
<td>11.20</td>
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<tr>
<td>mod.3+3 (c,ul=2)</td>
<td>21.35</td>
<td>3.72</td>
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<td>11.68</td>
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## Results - Scenario 5

### Recommendation as MTD in %

<table>
<thead>
<tr>
<th>Dose</th>
<th>≤ 9.3 mg</th>
<th>12.4 mg</th>
<th>16.53 mg</th>
<th>22 mg</th>
<th>29.4 mg</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3-Design</td>
<td>78.11</td>
<td>5.78</td>
<td>2.80</td>
<td>1.57</td>
<td>0.41</td>
<td>2.07</td>
</tr>
<tr>
<td>ADEPT(var,coh=2)</td>
<td>8.42</td>
<td>18.33</td>
<td><strong>24.14</strong></td>
<td>20.85</td>
<td>16.67</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=2)</td>
<td>9.52</td>
<td>17.94</td>
<td>24.05</td>
<td>21.62</td>
<td>15.86</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(var,coh=1)</td>
<td>10.22</td>
<td>18.09</td>
<td>23.68</td>
<td>20.98</td>
<td>15.82</td>
<td>0</td>
</tr>
<tr>
<td>ADEPT(pat,coh=1)</td>
<td>10.68</td>
<td>18.99</td>
<td>23.09</td>
<td>21.27</td>
<td>13.59</td>
<td>0</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=1)</td>
<td>40.68</td>
<td>11.29</td>
<td>12.77</td>
<td>8.39</td>
<td>11.15</td>
<td>2.08</td>
</tr>
<tr>
<td>mod.3+3 (D,ul=2)</td>
<td>52.69</td>
<td>9.18</td>
<td>7.25</td>
<td>5.02</td>
<td>11.15</td>
<td>2.07</td>
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<tr>
<td>mod.3+3 (c,ul=1)</td>
<td>46.40</td>
<td>11.08</td>
<td>11.16</td>
<td>7.95</td>
<td>9.47</td>
<td>2.07</td>
</tr>
<tr>
<td>mod.3+3 (c,ul=2)</td>
<td>52.22</td>
<td>9.32</td>
<td>7.48</td>
<td>5.07</td>
<td>11.27</td>
<td>2.07</td>
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## Results - Scenario 5 (cont.)

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<th>DLTs (mean)</th>
<th>patients treated above MTD (mean)</th>
<th>MSE</th>
</tr>
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<td>12.36</td>
<td>22.36</td>
<td>52.29</td>
</tr>
<tr>
<td>ADEPT(pat,coh=2)</td>
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<td>12.47</td>
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<td>52.28</td>
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<tr>
<td>ADEPT(var,coh=1)</td>
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<td>11.80</td>
<td>20.75</td>
<td>53.58</td>
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<td>ADEPT(pat,coh=1)</td>
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<td>11.84</td>
<td>17.65</td>
<td>50.47</td>
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<td>24.64</td>
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<td>113.83</td>
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<td>24.64</td>
<td>3.58</td>
<td>1.76</td>
<td>113.29</td>
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</table>
### Recommendation as MTD in %

<table>
<thead>
<tr>
<th>Dose</th>
<th>≤ 9.3 mg</th>
<th>12.4 mg</th>
<th>16.53 mg</th>
<th>22 mg</th>
<th>29.4 mg</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3-Design</td>
<td>31.83</td>
<td>23.95</td>
<td>13.80</td>
<td>6.33</td>
<td>0.72</td>
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</tr>
<tr>
<td>ADEPT(var,coh=2)</td>
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<td>42.56</td>
<td>22.29</td>
<td>1.79</td>
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<td>ADEPT(pat,coh=2)</td>
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<td>25.59</td>
<td>2.76</td>
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</tr>
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<td>22.46</td>
<td>1.61</td>
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</tr>
<tr>
<td>ADEPT(pat,coh=1)</td>
<td>1.07</td>
<td>23.18</td>
<td>41.94</td>
<td>25.26</td>
<td>2.16</td>
<td>0</td>
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<td>17.39</td>
<td>18.02</td>
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<td>6.98</td>
<td>0</td>
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<tr>
<td>mod.3+3 (D,ul=2)</td>
<td>19.13</td>
<td>24.42</td>
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<td>12.33</td>
<td>4.67</td>
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<tr>
<td>mod.3+3 (c,ul=1)</td>
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<td>17.61</td>
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<tr>
<td>mod.3+3 (c,ul=2)</td>
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<td>24.53</td>
<td>22.04</td>
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## Results - Scenario 6 (cont.)

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<th>DLTs (mean)</th>
<th>patients treated above MTD (mean)</th>
<th>MSE</th>
</tr>
</thead>
<tbody>
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<td>3.45</td>
<td>0.21</td>
<td>57.42</td>
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<td>ADEPT(var, coh=2)</td>
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<td>7.96</td>
<td>12.39</td>
<td>19.99</td>
</tr>
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<td>ADEPT(pat, coh=2)</td>
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<td>19.70</td>
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<td>10.94</td>
<td>19.66</td>
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<tr>
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<td>mod.3+3 (c, ul=1)</td>
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<td>47.08</td>
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<tr>
<td>mod.3+3 (c, ul=2)</td>
<td>34.40</td>
<td>4.25</td>
<td>1.99</td>
<td>49.51</td>
</tr>
</tbody>
</table>
Conclusions

- Bayesian ADEPT has highest 'hit rate' but also highest risk for patients
Conclusions

- Bayesian ADEPT has highest 'hit rate' but also highest risk for patients
  ⇒ not recommendable to use in practice when prior information is not available
Conclusions

- Bayesian ADEPT has highest 'hit rate' but also highest risk for patients
  ⇒ not recommendable to use in practice when prior information is not available
- 3+3-Design is most conservative, risk for patients is lowest
Conclusions

- Bayesian ADEPT has highest 'hit rate' but also highest risk for patients
  ⇒ not recommendable to use in practice when prior information is not available

- 3+3-Design is most conservative, risk for patients is lowest
  ⇒ safe to use, but high chance of underestimating the MTD
Conclusions

- Bayesian ADEPT has highest 'hit rate' but also highest risk for patients
  ⇒ not recommendable to use in practice when prior information is not available
- 3+3-Design is most conservative, risk for patients is lowest
  ⇒ safe to use, but high chance of underestimating the MTD
- Parametric modification of 3+3-Design has better 'hit rate' and only slightly increased risk for patients
Conclusions

- Bayesian ADEPT has highest 'hit rate' but also highest risk for patients
  ⇒ not recommendable to use in practice when prior information is not available

- 3+3-Design is most conservative, risk for patients is lowest
  ⇒ safe to use, but high chance of underestimating the MTD

- Parametric modification of 3+3-Design has better 'hit rate'
  and only slightly increased risk for patients
  ⇒ promising alternative
Future Work

- stopping rule: length of confidence interval for MTD
Future Work

- stopping rule: length of confidence interval for MTD
- fit proportional odds model (4 categories) instead of logistic model
References

- Gerke, O (2005): Optimal Phase I oncology trial design, Schering AG, First Clinical Statistics Europe Meeting
Thank you for your attention!

Questions?