A Bayesian dose-finding procedure applied to a seamless Phase I/II trial in rheumatoid arthritis

Anne Whitehead, Helene Thygesen, John Whitehead
MPS Research Unit, Lancaster University
Email: p.a.whitehead@lancaster.ac.uk

Vladimir Dragalin
Aptiv Solutions, Morrisville, NC, USA

Outline

1. **Trial in rheumatoid arthritis**
2. **Bayesian model**
3. **Criteria for dose escalation**
4. **Choice of prior distribution**
5. **Simulation study to evaluate procedure**
6. **Discussion**

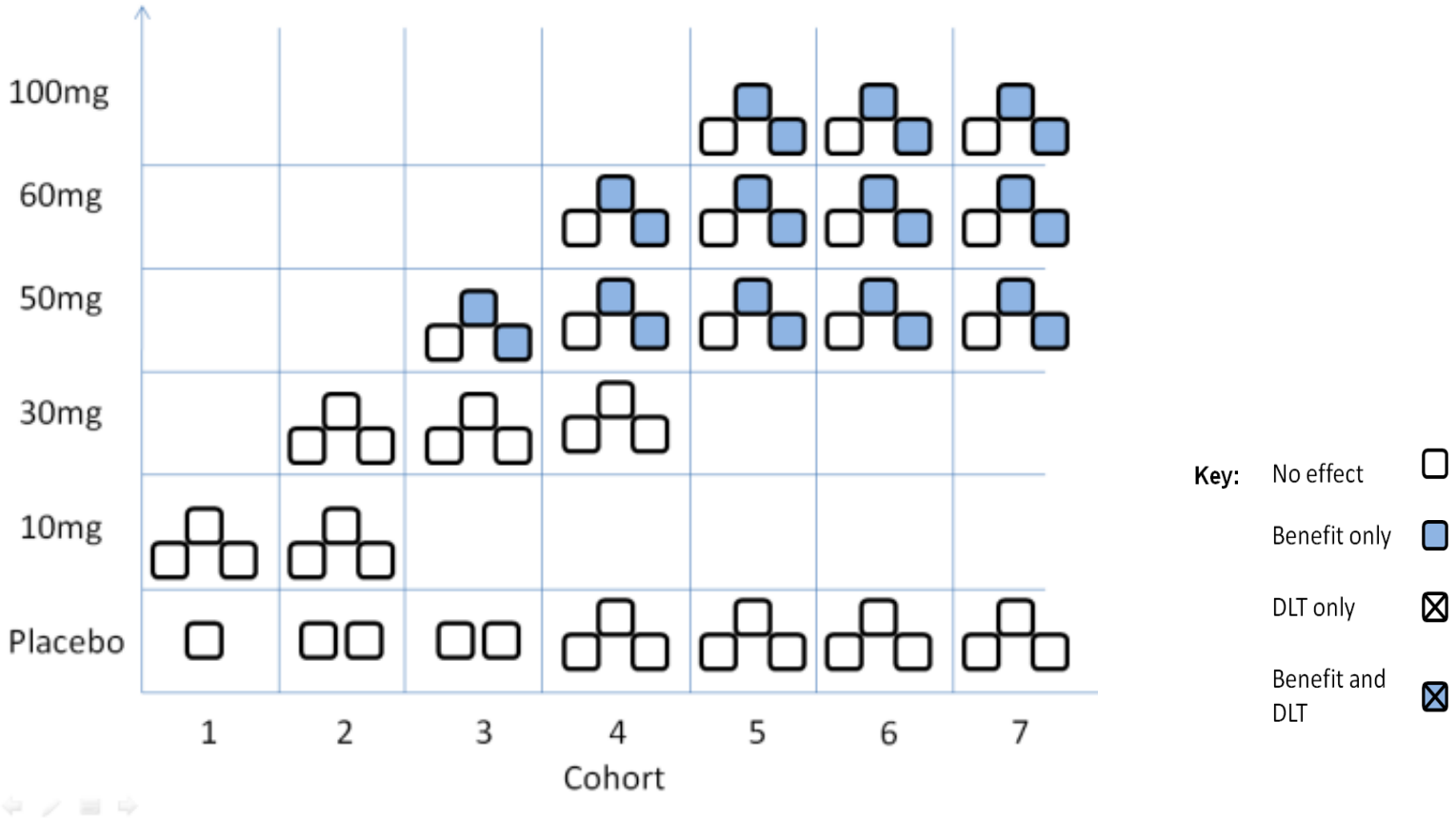
1. Trial in rheumatoid arthritis

- **Dose levels – 0 (placebo), 10, 30, 50, 60, 100 mg every four weeks**
- **Safety outcome – Occurrence of a dose limiting toxicity (DLT) within 4 weeks**
- **Primary efficacy outcome – Success on ACR20 at 16 weeks**
- **Early efficacy indicator – Success on ACR20 at 4 weeks and 25% reduction in CRP at 4 weeks**

Phase I/II design

- **Randomise first cohort between placebo and 10 mg**
- **If 10 mg dose appears safe, randomise second cohort between placebo, 10 mg and 30 mg**
- **Continue to open up higher doses to randomisation unless there are safety concerns**
- **Cease randomisation to doses with safety concerns**
- **Cease randomisation to doses if early efficacy indicator shows they are no better than placebo (futility)**
- **Randomisation ends when 33 patients recruited to each dose considered both safe and non-futile**
- **Patients followed up for 16 weeks and definitive analysis based on primary efficacy outcome for all completers**

Example

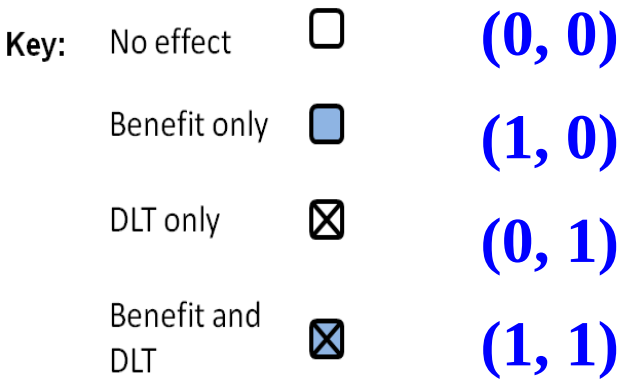

100mg
60mg
50mg
30mg
10mg
Placebo
1
2
3
4
5
6
7
Cohort
Key:
No effect
Benefit only
DLT only
Benefit and DLT

2. Bayesian model

- **k doses of drug available for testing: $d_1 < \ldots < d_k$**

  d_0 = placebo

- **Bivariate outcome (i, j) for (benefit, harm)**



Bayesian model

- **Risks $r_x(i, j)$ = probability of outcome (i, j) from dose d_x**
- **$r_x(i, j)$ treated as random variables and modelled directly**
- **Assume $r_x(i, j)$ is equal to one of a grid of h values**

$$b_1 < \ldots < b_h$$

For rheumatoid arthritis trial

b_1	b_2	b_3	b_4	b_5
0.05	0.25	0.45	0.65	0.85

Marginal probabilities of benefit or harm

0.1	0.3	0.5	0.7	0.9

Monotonicity constraint

- **Probability of benefit $r_x(1, *) = r_x(1, 0) + r_x(1, 1)$ non-decreasing with dose**
- **Probability of harm $r_x(*, 1) = r_x(0, 1) + r_x(1, 1)$ non-decreasing with dose**
- **Probability of benefit and harm $r_x(1, 1)$ non-decreasing with dose**
- **Probability of no effect $r_x(0, 0)$ non-increasing with dose**

Prior and posterior distributions of the $r_x(i, j)$

Admissible values of $r_x(i, j)$ are one of the five values (0.05, 0.25, 0.45, 0.65, 0.85) subject to the monotonicity constraint

Prior and posterior distributions of $r_x(i, j)$ take positive values for admissible risk values and 0 otherwise

3. Criteria for dose escalation

- **A cohort of new patients is ready for treatment**

- **Allocate 3 patients to each of the p permissible doses**
- **Allocate p patients to placebo**
- **Cohort size = 4p**

- **Safety criterion $P(r_x(*, 1) = 0.7 \text{ or } 0.9) \leq 0.1$**

- **Futility criterion $P(r_x(1, *) = r_0(1, *)) \geq 0.85$**

4. Choice of prior distribution

A class of conjugate priors $h_0(r)$ can be created by defining

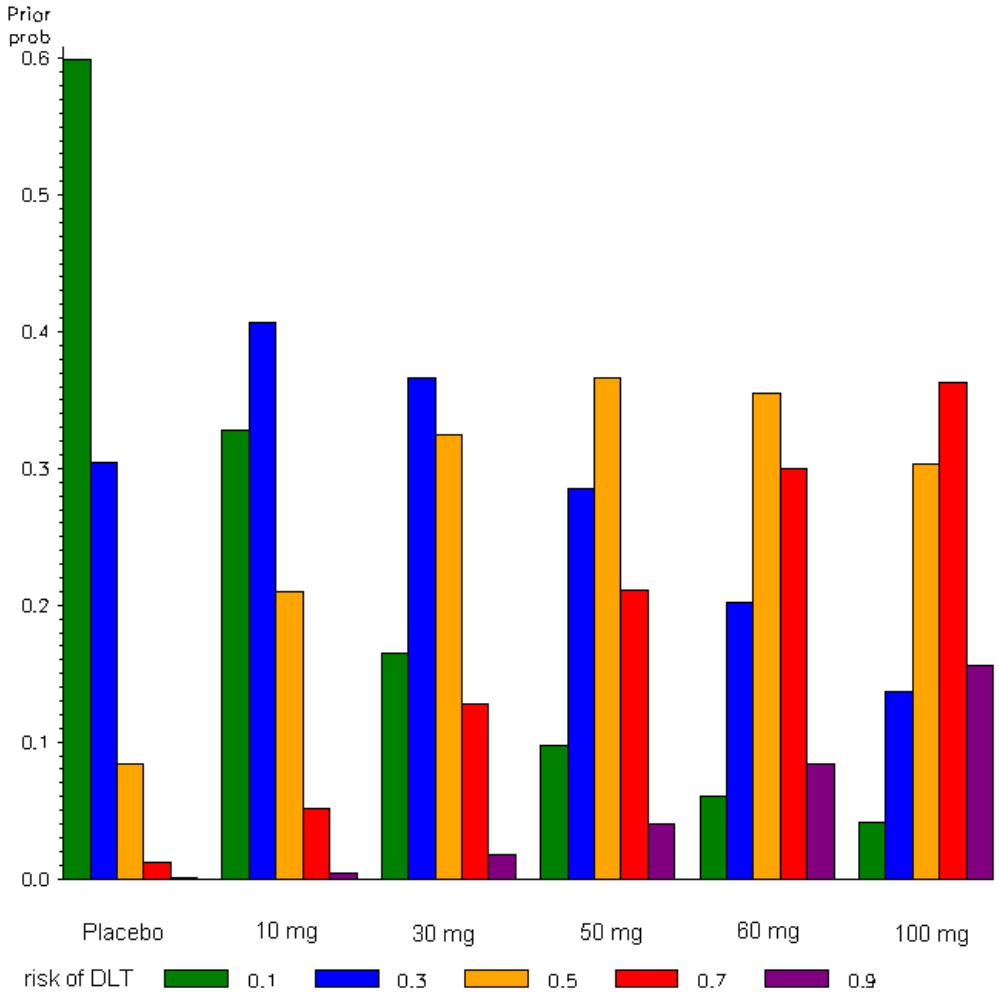
$$\log\left\{h_0\left(\mathbf{r}\right)\right\} = \text{const} + \sum_x \sum_i \sum_j a_x(i, j) \log\left(r_x(i, j)\right)$$

for suitable values of $a_x(i, j)$

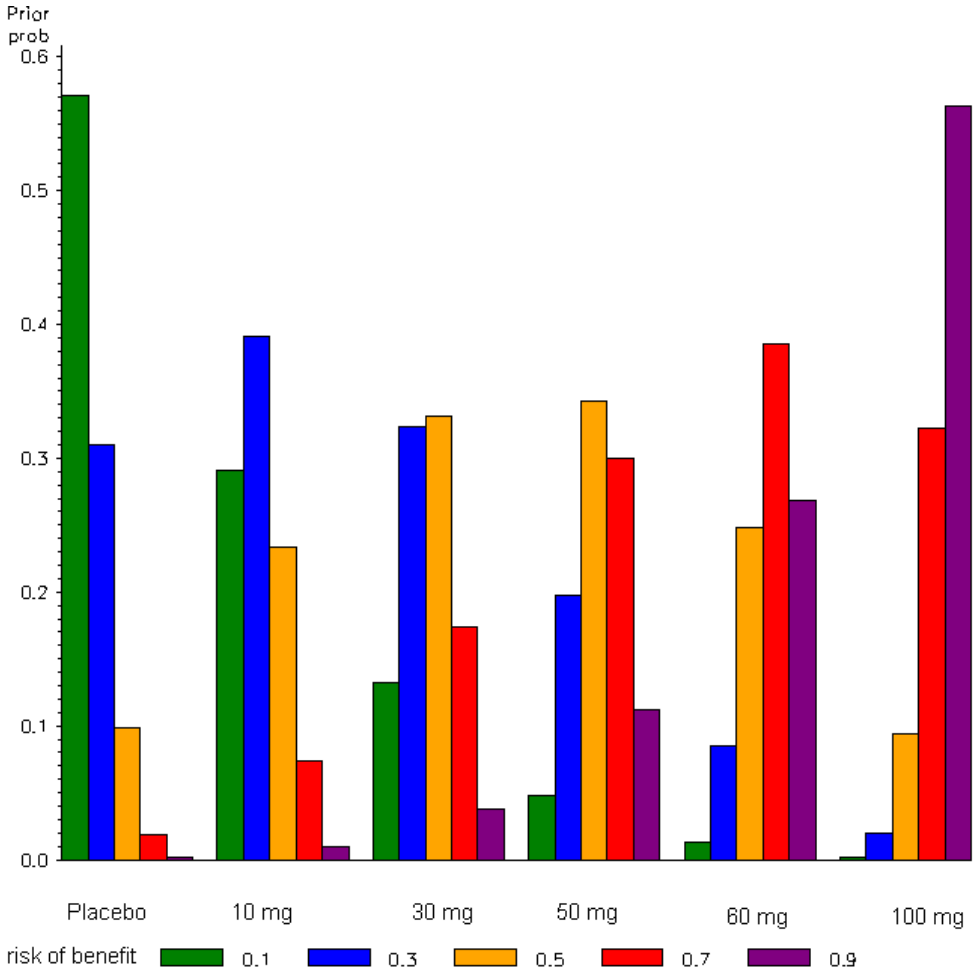
Chosen values of $a_x(i,j)$

		Dose					
Benefit	**Harm**	**0**	**10**	**30**	**50**	**60**	**100**
0	**0**	**0**	**0**	**− 0.125**	**0**	**0**	**0.750**
1	**0**	**0**	**0**	**− 0.125**	**0**	**0**	**0.750**
0	**1**	**0**	**0**	**0.125**	**0**	**0**	**− 0.750**
1	**1**	**0**	**0**	**0.125**	**0**	**0**	**− 0.750**

Marginal prior densities for DLT risk



Marginal prior densities for risk of benefit



5. Simulation study to evaluate procedure

- **log(CRP4/CRP0)**
  - ***a function of dose***
- **logit(P(Success on ACR20 at 4 weeks))**
  - ***a function of dose and log(CRP4/CRP0)***
- **logit(P(Success on ACR20 at 16 weeks))**
  - ***a function of dose, log(CRP4/CRP0) and ACR20 at 4 weeks***
- **logit(P(DLT at 4 weeks))**
  - ***a function of dose and log(CRP4/CRP0)***

- **Dose considered safe if true DLT risk ≤ 0.5**
- **Dose x considered futile if true week 4 P(benefit) values give P(benefit on dose x) < P(benefit on placebo) + 0.2**
- **1000 simulations per scenario**

Scenario 1 –Effective and low DLT risk

	% of patients (true value)			No. of patients	% times dose found		
Dose	**DLT risk**	**Efficacy at week 4**	**Efficacy at week 16**	**Average treated**	**Unsafe**	**Futile**	**Permissible + sig efficacy at week 16**
Placebo	**1**	**8**	**18**	**54**			
10 mg	**3**	**29**	**50**	**31**	**0.2**	**10.7**	**74.4**
30 mg	**6**	**40**	**67**	**33**	**0.8**	**0.6**	**98.0**
50 mg	**8**	**45**	**73**	**33**	**0.9**	**0**	**99.1**
60 mg	**9**	**47**	**76**	**33**	**1.0**	**0**	**99.0**
100 mg	**12**	**51**	**80**	**32**	**3.0**	**0**	**97.0**

Scenario 2 – Effective and moderate DLT risk

	% of patients (true value)			No. of patients	% times dose found		
Dose	**DLT risk**	**Efficacy at week 4**	**Efficacy at week 16**	**Average treated**	**Unsafe**	**Futile**	**Permissible + sig efficacy at week 16**
Placebo	**6**	**7**	**18**	**37**			
10 mg	**15**	**26**	**43**	**29**	**3.0**	**19.4**	**46.7**
30 mg	**24**	**41**	**59**	**30**	**9.2**	**1.6**	**83.5**
50 mg	**28**	**49**	**67**	**26**	**23.2**	**0.1**	**75.4**
60 mg	**30**	**52**	**69**	**18**	**48.5**	**0**	**51.4**
100 mg	**35**	**59**	**76**	**9**	**74.4**	**0**	**25.6**

Scenario 3 –Mostly futile and low DLT risk

	% of patients (true value)			No. of patients	% times dose found		
Dose	**DLT risk**	**Efficacy at week 4**	**Efficacy at week 16**	**Average treated**	**Unsafe**	**Futile**	**Permissible + sig efficacy at week 16**
Placebo	**1**	**6**	**17**	**46**			
10 mg	**3**	**14**	**36**	**18**	**0**	**72.8**	**14.2**
30 mg	**5**	**19**	**48**	**26**	**0.2**	**39.1**	**53.3**
50 mg	**7**	**21**	**54**	**30**	**0.5**	**16.7**	**75.6**
60 mg	**8**	**23**	**57**	**32**	**0.8**	**7.4**	**87.0**
100 mg	**10**	**25**	**63**	**32**	**1.1**	**1.8**	**95.3**

Scenario 4 –Effective and high DLT risk

	% of patients (true value)			No. of patients	% times dose found		
Dose	DLT risk	Efficacy at week 4	Efficacy at week 16	Average treated	Unsafe	Futile	Permissible + sig efficacy at week 16
Placebo	0	7	18	26			
10 mg	8	26	43	29	0.8	20.7	37.0
30 mg	29	41	59	29	14.5	2.0	72.6
50 mg	46	49	67	17	56.2	0.4	43.0
60 mg	53	52	69	3	96.0	0	4.0
100 mg	71	59	76	0.05	100.0	0	0

6. Discussion

- **A dose finding method for phase I/II trials based on both safety and efficacy outcomes has been presented**

- **Bayesian approach requires specification of**
  - ***Grid prior for bivariate risks*** $\{b_1, \ldots, b_h\}$
  - ***Criteria for dose escalation***
  - ***Characteristics of prior distribution***

- **Adapted for a specific trial**
  - ***Includes placebo***
  - ***Parallel recruitment to all permissible dose levels***
  - ***Demonstrated satisfactory operational characteristics***

Discussion

- **The approach**
  - ***Provides model parameters with simple interpretation***
  - ***Avoids reliance on a parametric model***
  - ***Can be applied automatically***
  - ***Provides guidance to Safety Committee***
  - ***Can use conjugate prior to specify prior belief***
  - ***Elicitation of investigators' prior beliefs undertaken in terms of operation of procedure under simplified scenarios***
  - ***Has potential for generalisation***