Practical Implementation of a Model-based Dose-finding Design in a Phase I Combination-Schedule Trial

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Motivating Trial

- Phase I Combination Trial in Oncology
- Two compounds:
  - Approved agent N (two doses)
  - Experimental agent M1774 (five doses)
- Two administration schedules of M1774
  - Continuous once daily dosing
  - A schedule with breaks from treatment ($\sim$ half as intensive)
- The primary objective: study safety and find MTC

Challenges

- Unknown ordering for some combinations;
- 3-dimensional dose-finding problem;
- How to model combination-*schedules*.
- Twenty combination-schedules (some might not be tried);
- Use the model beyond this trial.

$\rightarrow$ The **partial ordering continual reassessment method** (POCRM) by N Wages et.al (2011).

Partial Ordering Continual Reassessment Method

- R feasible orderings of the regimens;
- r – index of ordering, $r = 1, \ldots, R$;
- i – index of the regimen, $i = 1, \ldots, 20$;
- π_{ir} – standardised regimen level;
- p_{ir} – probability of a DLT.

$$p_{ir} = \pi_{ir}^{\exp(\alpha_r)}.$$

Models π_{ir} are constructed from a skeleton $\tilde{\pi}_i$ by re-ordering it.

Toy Example

Agents A and B; two doses of each.

$(A_1; B_2)$	$(A_2; B_2)$
$(A_1; B_1)$	$(A_2; B_1)$

Skeleton: $\pi = (0.10, 0.20, 0.30, 0.40)$

	Combinations			
Ordering	$(A_1; B_1)$	$(A_2; B_1)$	$(A_1; B_2)$	$(A_2; B_2)$
1	$(0.10)^{\alpha_1}$	$(0.20)^{\alpha_1}$	$(0.30)^{\alpha_1}$	$(0.40)^{\alpha_1}$
2	$(0.10)^{\alpha_2}$	$(0.30)^{\alpha_2}$	$(0.20)^{\alpha_2}$	$(0.40)^{\alpha_2}$

Design

1. The first cohort is allocated to the starting regimen;
2. DLT outcomes evaluated.
3. POCRM fits a model under each of the R orderings.
4. Ordering with the highest posterior probability of being the true one is selected.
5. The inference for combination-toxicity relationship is made under this ordering (subject to escalation constraint).
6. Steps 2–5 are repeated.

How to choose orderings

- Specify combination-schedule grid

Combination-Schedule Grid

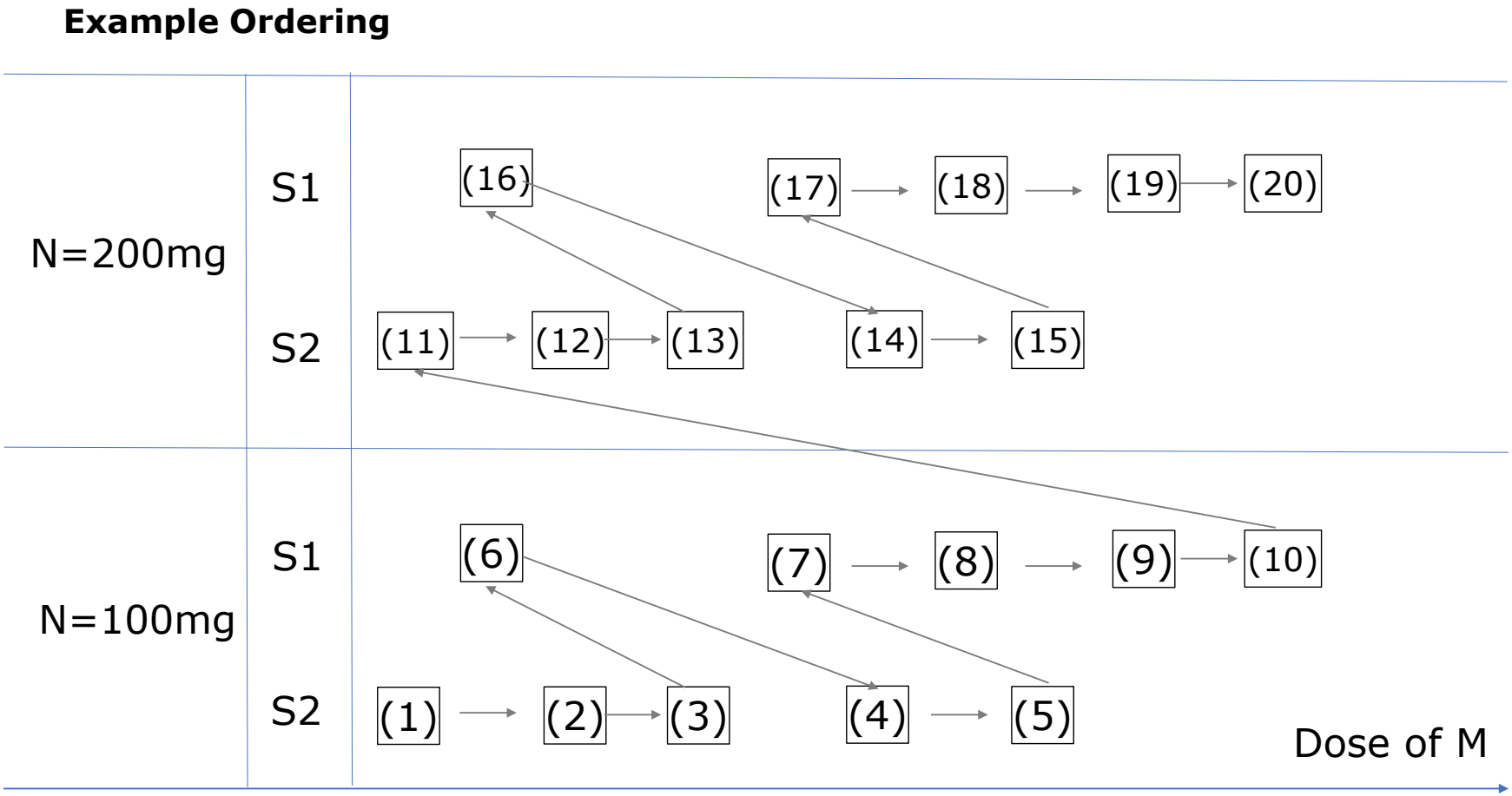
	S1 (16) N=200 M=30 [210]			S1 (17) N = 200 M=60 [420]		S1 (18) N=200 M=90 [630]		S1 (19) N=200 M=130 [910]	S1 (20) N=200 M=180 [1260]
S2 (11) N=200 M=30 [105]		S2 (12) N=200 M=60 [210]	S2 (13) N=200 M=90 [315]		S2 (14) N=200 M=130 [455]		S2 (15) N=200 M=180 [630]		
	S1 (6) N=100 M=30 [210]			S1 (7) N=100 M=60 [420]		S1 (8) N=100 M=90 [630]		S1 (9) N=100 M=130 [910]	S1 (10) N=100 M=180 [1260]
S2 (1) N=100 M=30 [105]		S2 (2) N=100 M=60 [210]	S2 (3) N=100 M=90 [315]		S2 (4) N=100 M=130 [455]		S2 (5) N=100 M=180 [630]		

How to choose orderings

- Specify combination-schedule grid;
- Discuss possible drivers of toxicity with clinicians;
- Provide first set of orderings
  - Start from statistical considerations (Wages et.al 2014);
  - Add clinically plausible orderings;
  - Supply with assumptions that stand behind each one;
  - Illustrate with a figure.

Example ordering

N is the main driver of toxicity, then M1774 schedule (low to moderate difference), then the total average amount of M1774.



How likely each of the orderings is?

- PO-CRM requires prior probability of each ordering
- Eliciting these for a large orderings can be challenging.
- Elicit **probabilities for pairs** of the anti-diagonal regimens; *[Regimens (12) & (16) have the same total average dose of M774 and N, but less intensive schedule yet higher single M1774 dose.]*
- Find **probabilities of orderings** consistent with these.

PO-CRM Parameters and Evaluations

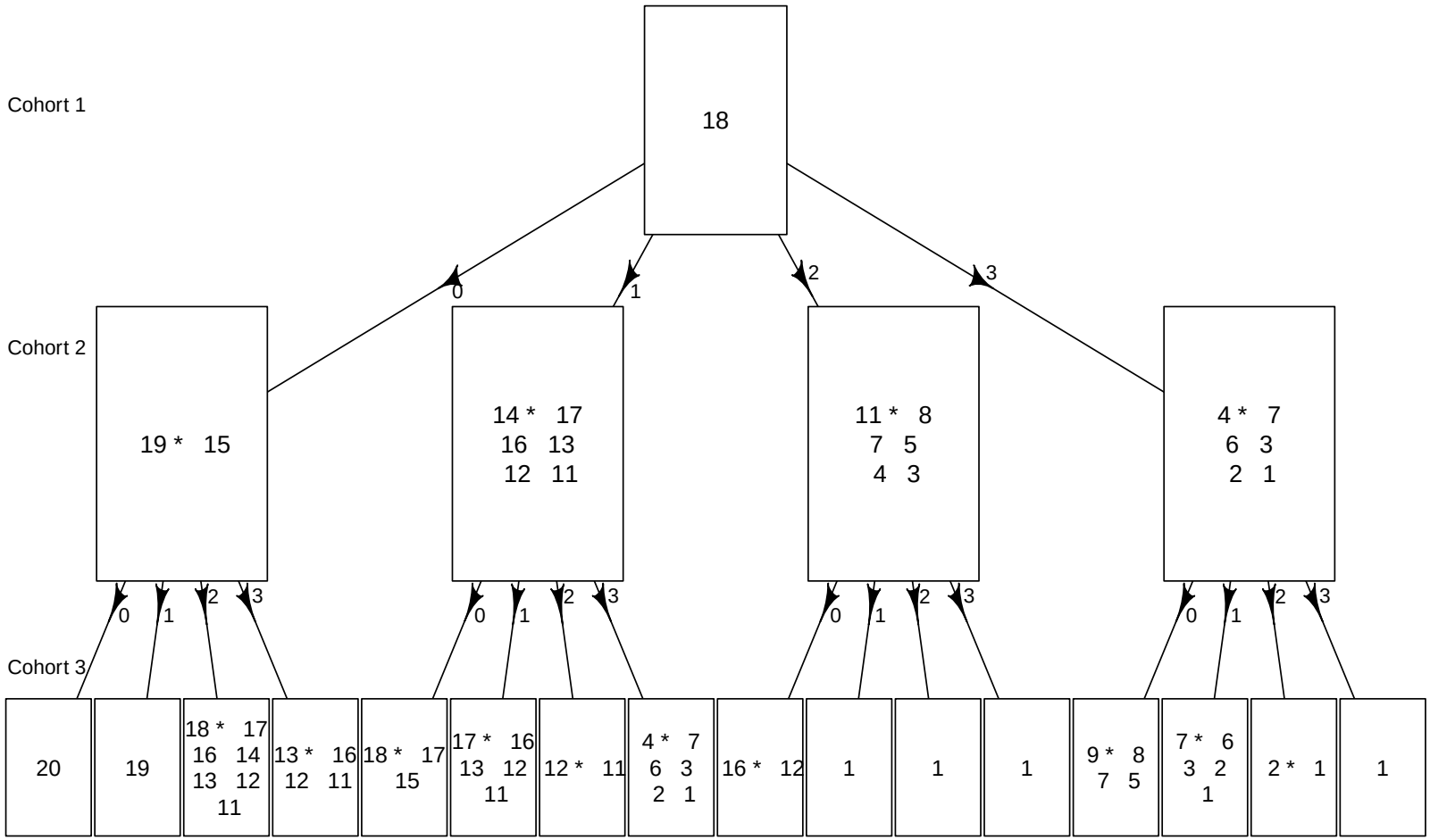
- The parameters of the design were defined via calibration
  - High accuracy and good safety;
  - Intuitive escalation/de-escalation decisions;

- Means of the evaluation:
  - Output in hypothetical scenarios;
  - Decision-Tree;
  - Extensive simulation study
    - Possibility to overrule the model recommendation.

Example output

	200N, 30M, S1 n=0 T= 0 Mean=0.14 Over=13.8% Trgt=20.4%			200N, 60M, S2 n=0 T= 0 Mean=0.17 Over=18.4% Trgt=23.5%		200N, 90M, S2 n=3 T= 1 Mean=0.31 Over=41.2% Trgt=26.9%
200N, 30M, S2 n=0 T= 0 Mean=0.06 Over=5.5% Trgt=11.6%		200N, 60M, S2 n=0 T= 0 Mean=0.08 Over=7.5% Trgt=14.3%	200N, 90M, S2 n=0 T= 0 Mean=0.11 Over=10.2% Trgt=17.3%		200N, 130M, S2 n=0 T= 0 Mean=0.21 Over=24.4% Trgt=26.3%	
	100N, 30M, S1 n=0 T= 0 Mean=0 Over=0.3% Trgt=1.2%			100N, 60M, S1 n=0 T= 0 Mean=0 Over=0.5% Trgt=1.9%		100N, 90M, S1 n=0 T= 0 Mean=0.02 Over=1.9% Trgt=5.4%
100N, 30M, S2 n=0 T= 0 Mean=0 Over=0% Trgt=0%		100N, 60M, S2 n=0 T= 0 Mean=0 Over=0.1% Trgt=0.3%	100N, 90M, S2 n=0 T= 0 Mean=0 Over=0.1% Trgt=0.7%		100N,130M, S2 n=0 T= 0 Mean=0 Over=0.8% Trgt=2.8%	

Decision tree



Conclusion

- Establishing of optimal doses & schedules is paramount;
- Model-based designs support a more efficient decision-making by borrowing of information;
- Close & constant collaboration with the trial team is a key;
- Various illustration tools to communicate properties;
- Has been reviewed by FDA & MHRA, and now implemented;
- Such designs take resources but it will pay off in development.