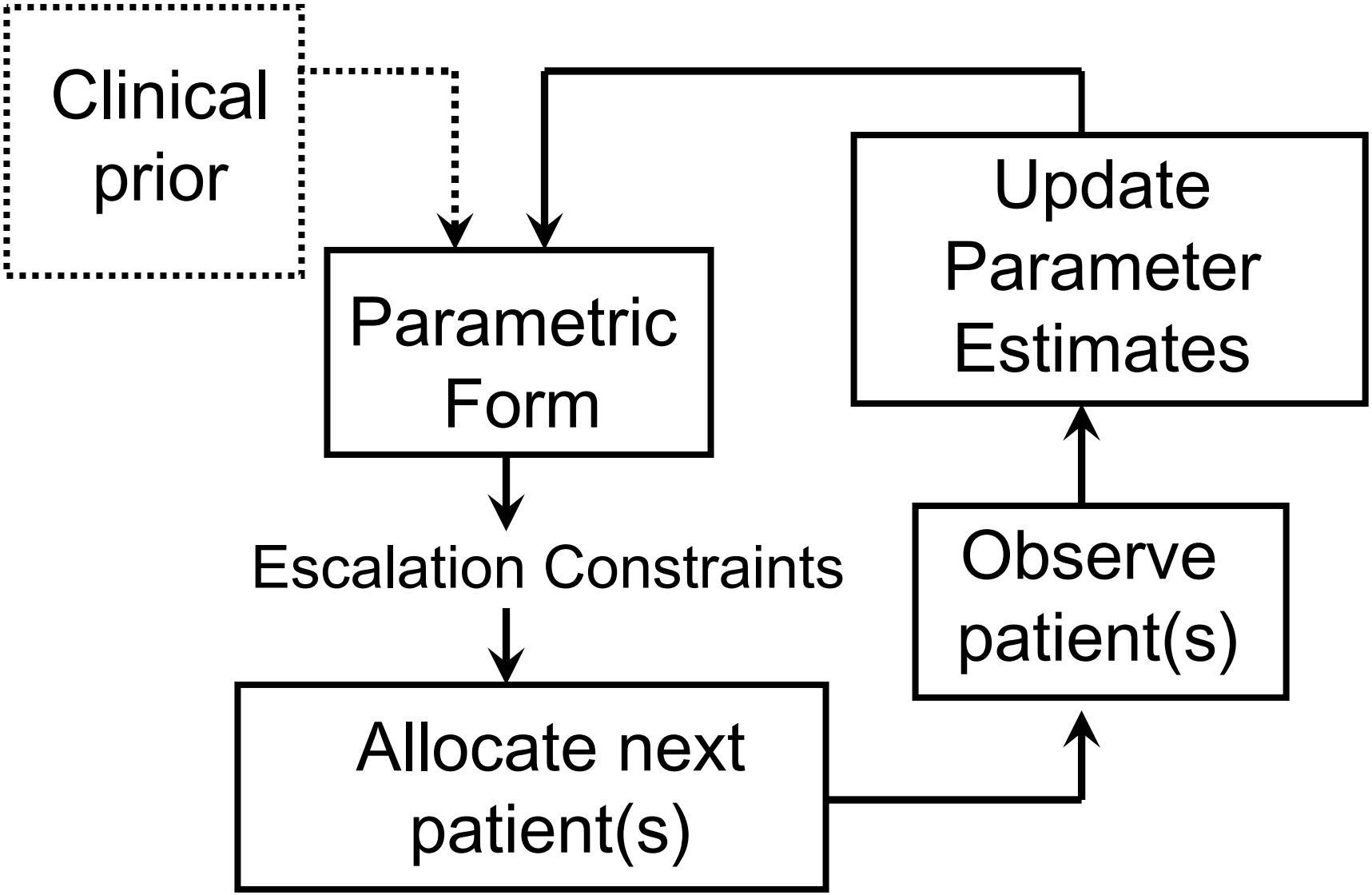
Adaptive Designs In Two Dimensions: An Example In Oncology

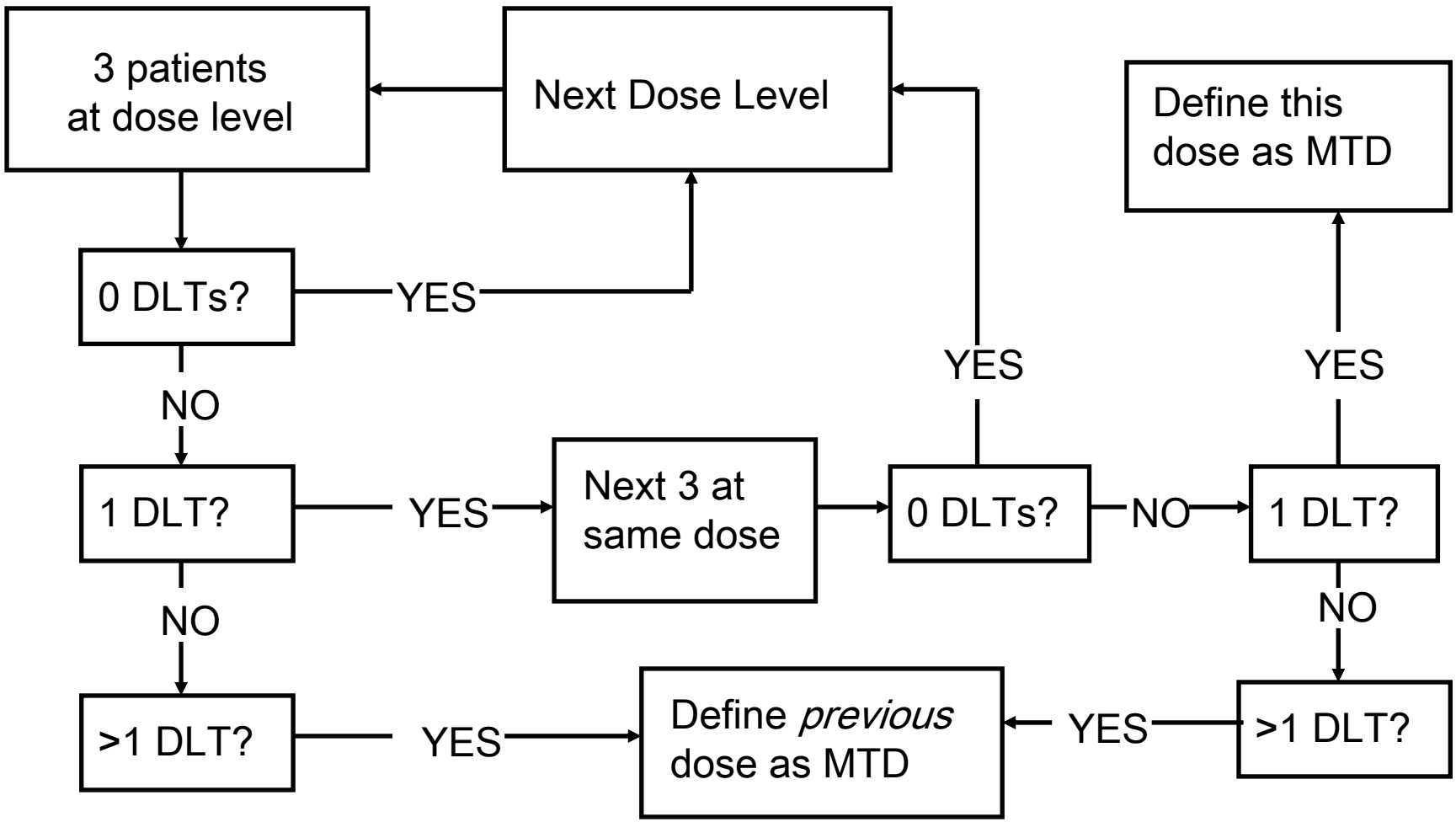
PAGE 2004

James G Wright, Clet Niyikiza, Alan Boddy, Chris Twelves and Hilary A Calvert

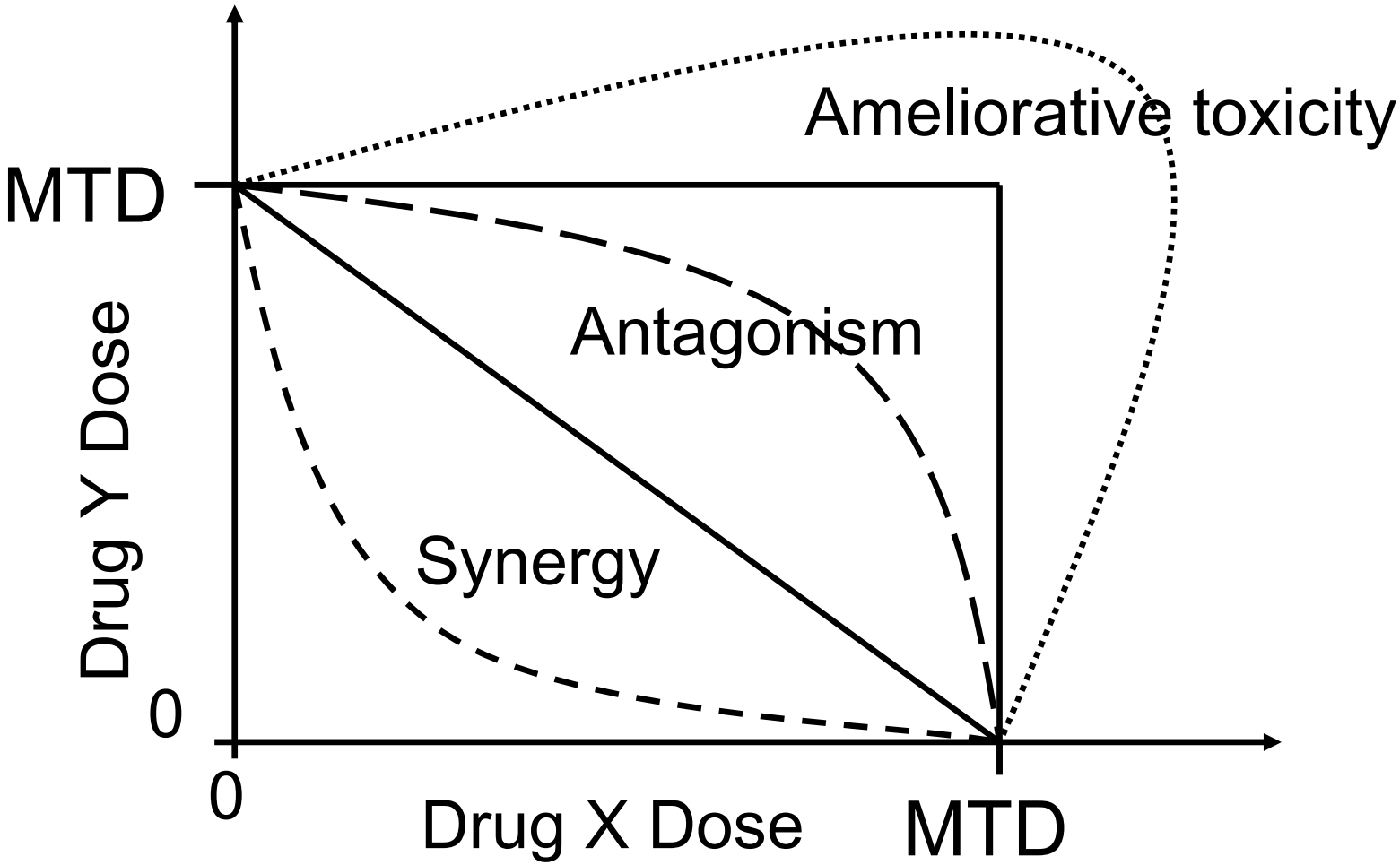
The Continual Reassessment Method



The traditional phase I trial is a Markov chain



Toxicity contours in 2D



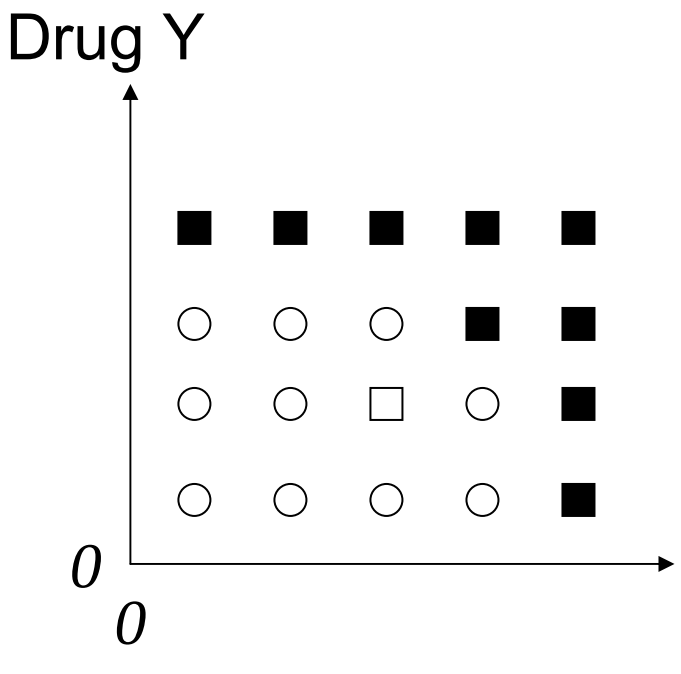
- Consider efficacy to focus patient “chains” on desirable regions of the MTD contour

An (arbitrary) parametric form

$$\Pr(DLT) = \frac{\exp(a + bx + cy + dxy)}{1 + \exp(a + bx + cy + dxy)}$$

- Pr(DLT) is a *nonlinear* function of combined dose.
- Quadratic form describes interaction between the drug doses
- We should avoid ameliorative toxicity in dose escalation trials.
- Therefore, d is constrained for the dose space.

Escalation constraints are critical for protocol approval



□ A dose administered without DLT

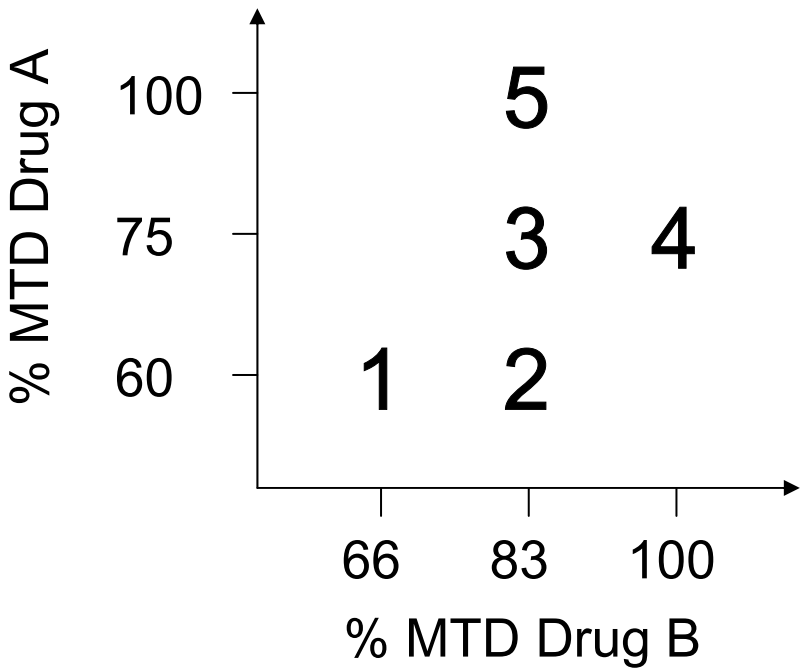
○ Doses which this dose (□) implies are available

■ Doses that are still unavailable

- The model shares information among chains – restraining to doses with Pr(DLT)<0.3.

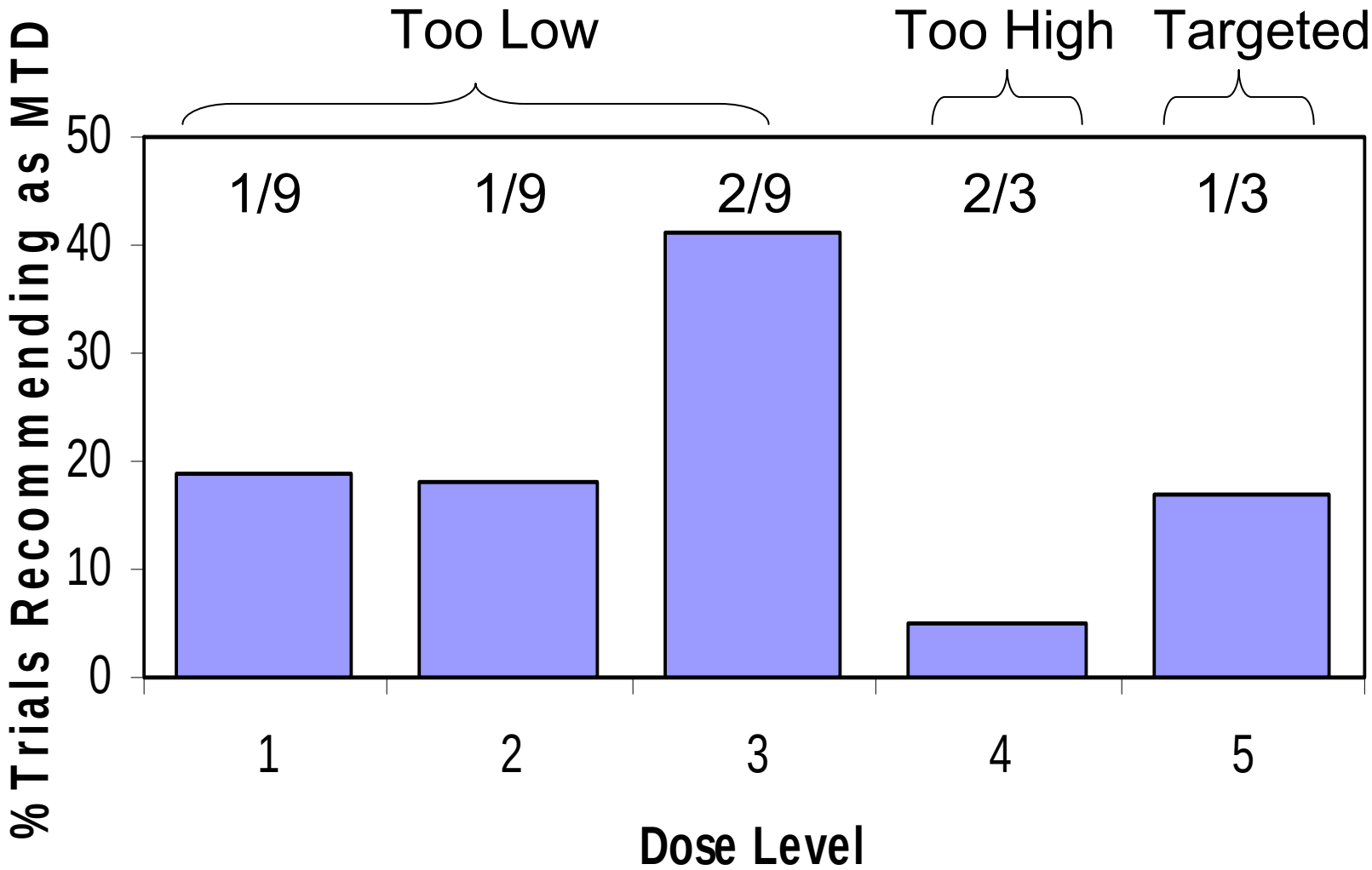
An example

- Data from a traditional Phase I trial were resampled for DLTs at each dose combination explored.
- 2D CRM and actual trial design compared on identical sequences.

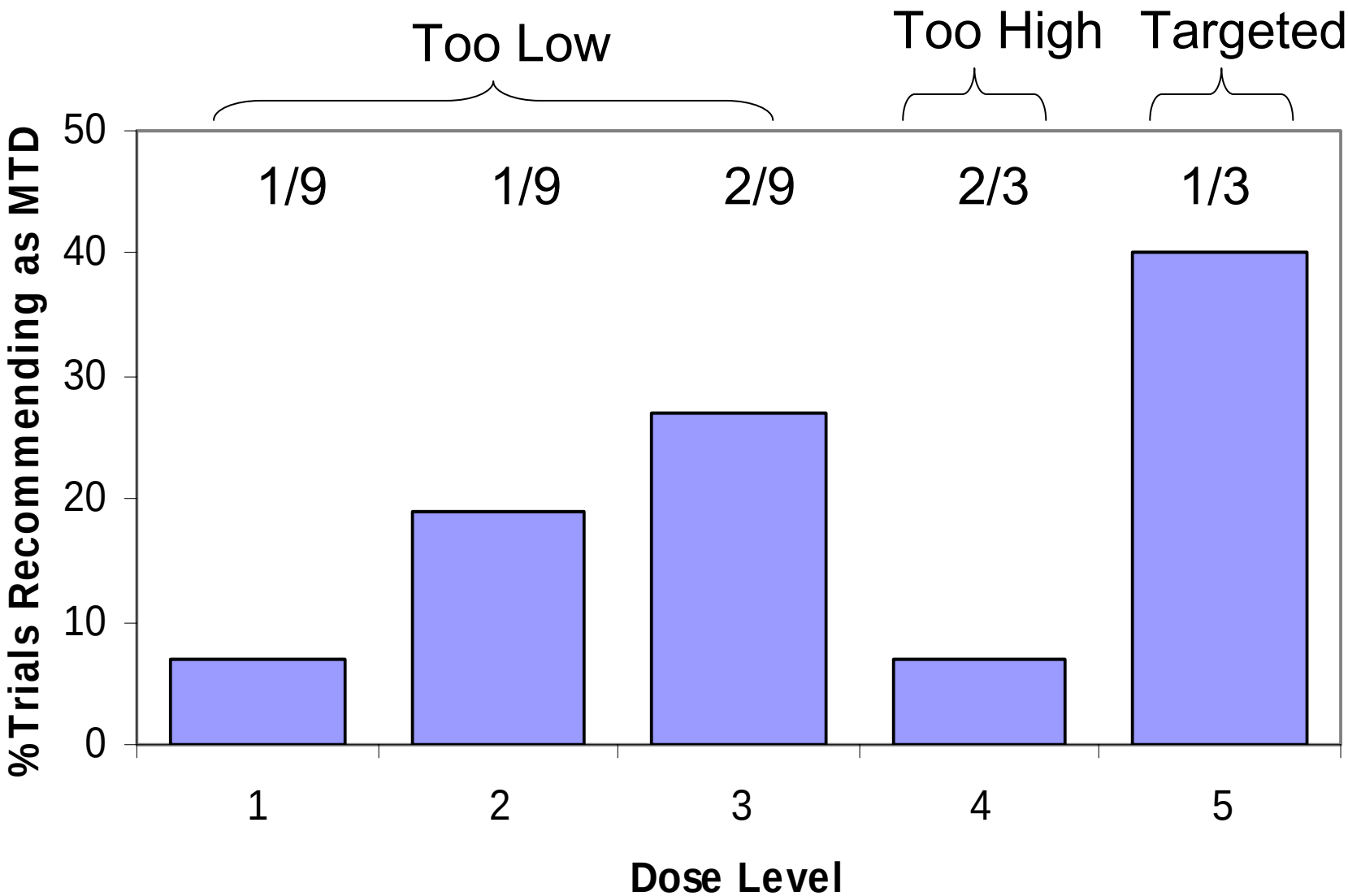


Level	Pr (DLT)
1	1/9 *
2	1/9 *
3	2/9
4	2/3
5	1/3

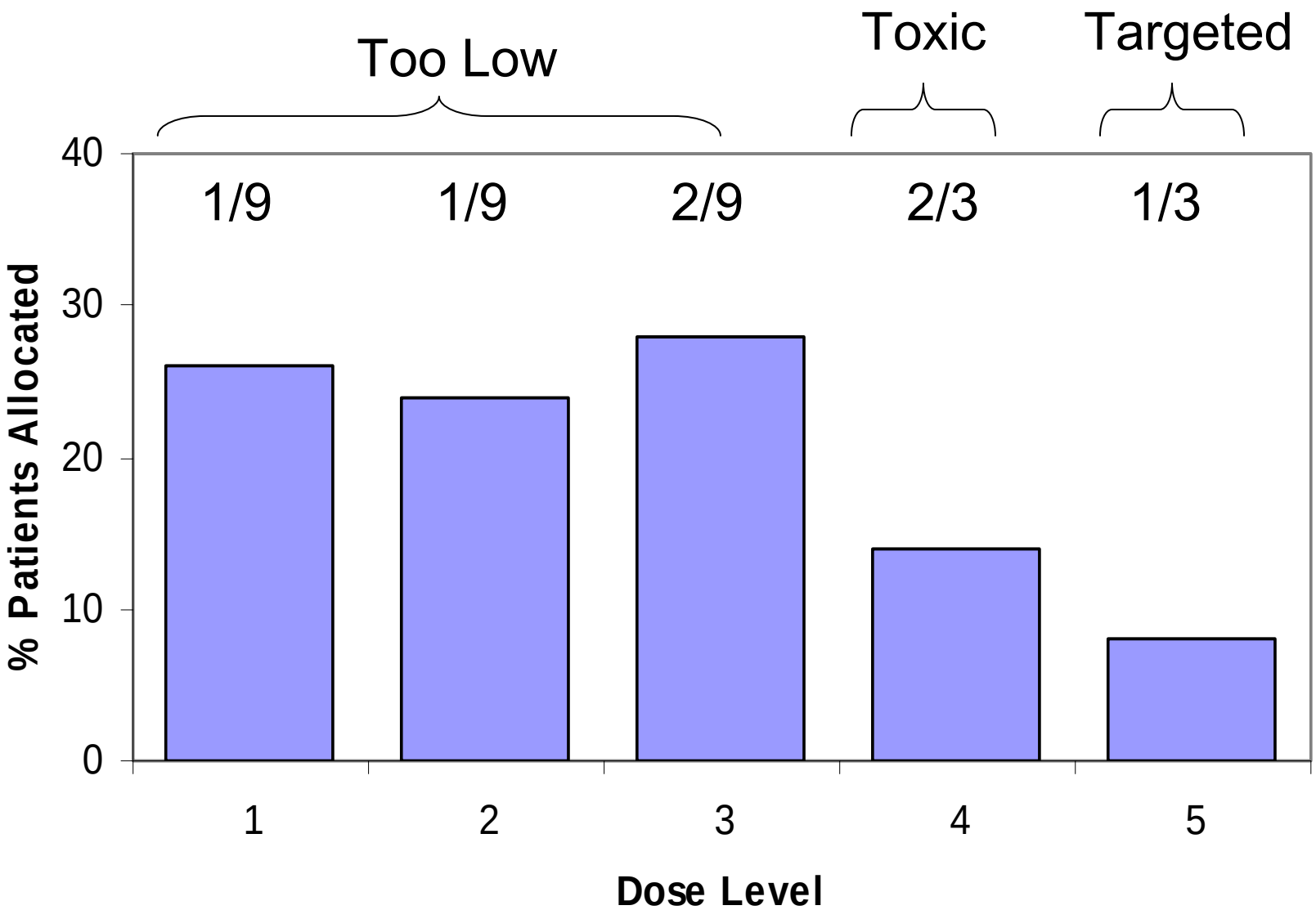
Traditional Trial MTD recommendations



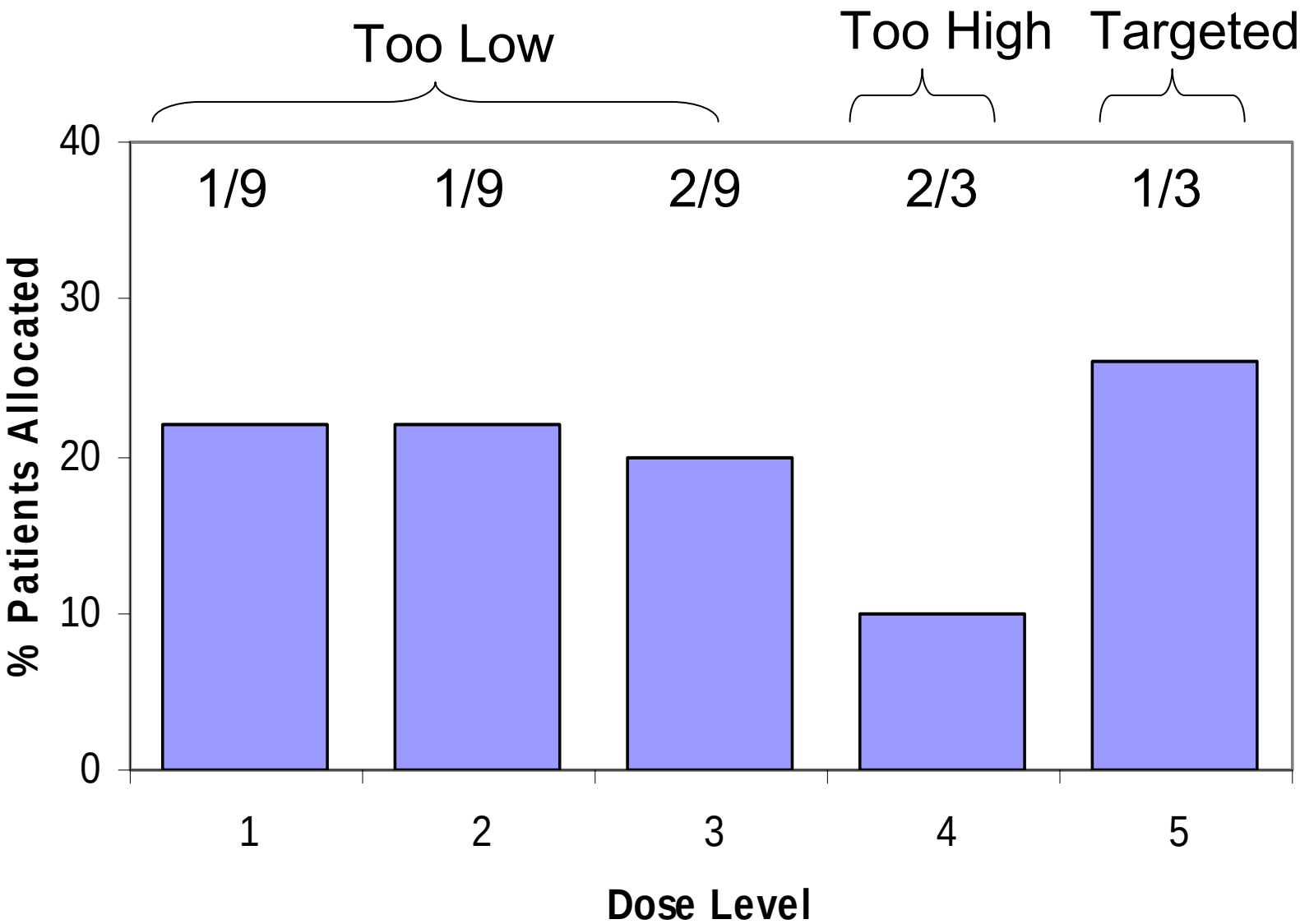
2D CRM MTD recommendations



Patient allocation with Traditional Design



Patient allocation with 2D CRM



Simulation inference

- Only 2 doses that are not ordered in one dimension, yet MTD estimates improved by acknowledging dimensionality.
- The 2D CRM treats more patients at the eventual MTD - and fewer at toxic doses
- Stopping criterion would yield further improvements
- The success of future trials is conditioned on the estimate of MTD in phase I trials…

Novel agent combination trial

- Prospective implementation, so genuine 2D design.
- Multiple chains can share information and avoid “recruitment closure”.
- Investigators Prof Hilary Calvert and Dr Chris Twelves provided priors for the dose levels.
- Initial simulations using priors led to modification of original design.

Table: Registration of prior expectation that DLT will occur at that dose level

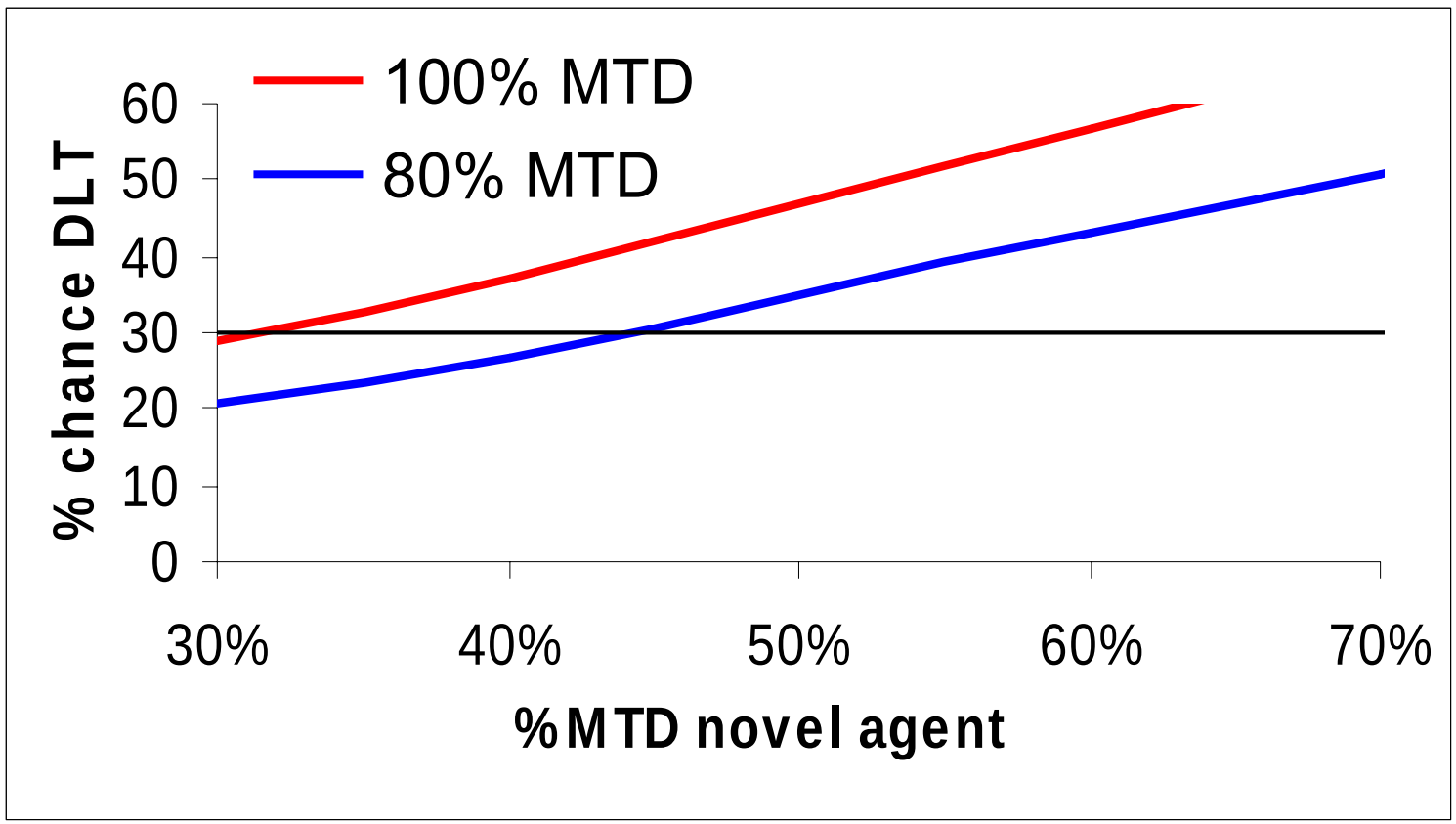
% of MTD	30%	40%	50%	60%	70%	80%	100 %
80%	___ out of ___	___ out of ___	___ out of ___	___ out of ___	___ out of ___	___ out of ___	___ out of ___
100%	___ out of ___	___ out of ___	___ out of ___	___ out of ___	___ out of ___	___ out of ___	___ out of ___

Investigator:_____

Location: _____

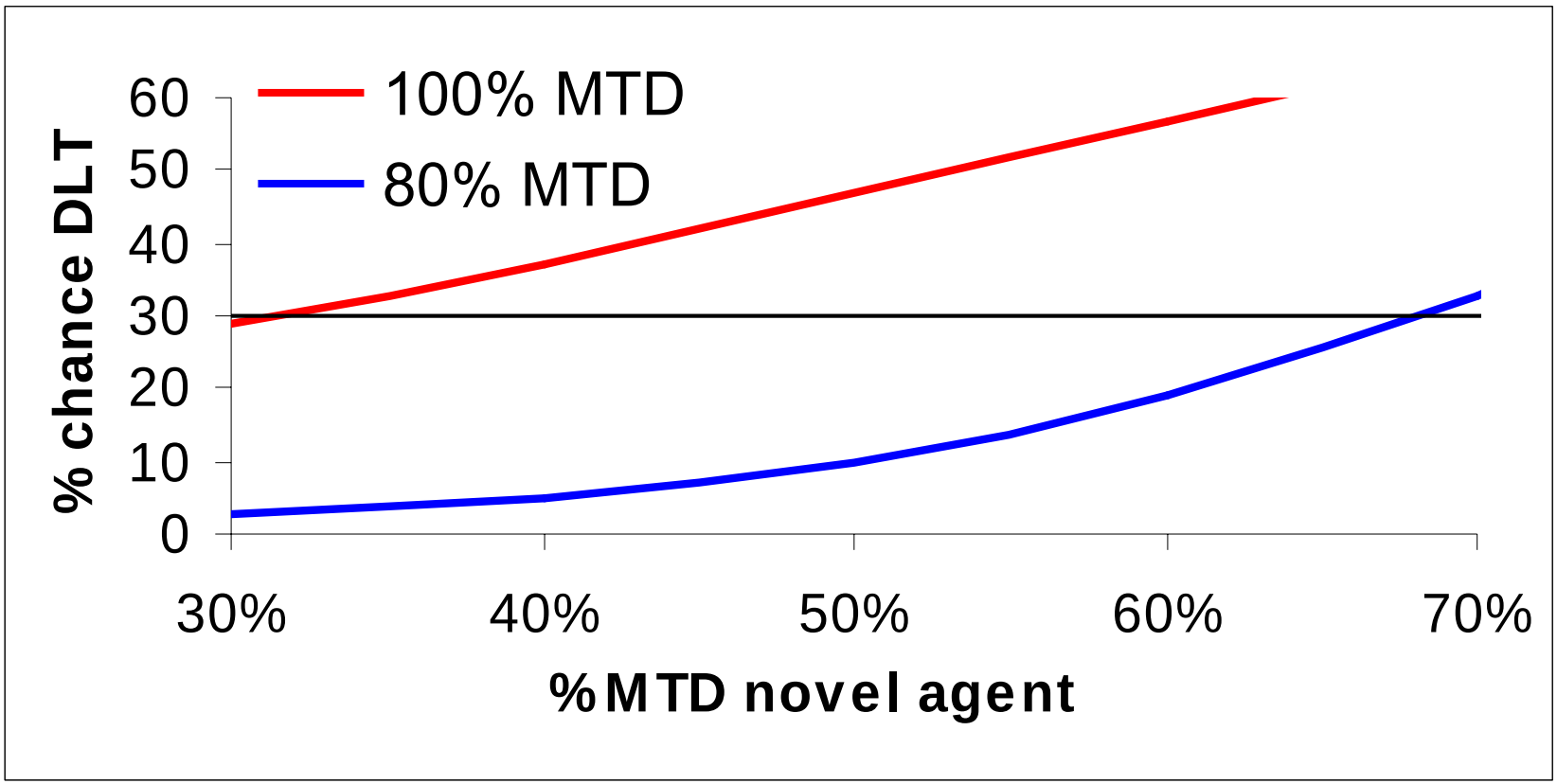
Signature: _____ Date: _____

- Survey results downweighted by a factor of 145, in order to to comply with the dose escalation scheme in the absence of toxicity.
- Hence, weightings only used relatively.



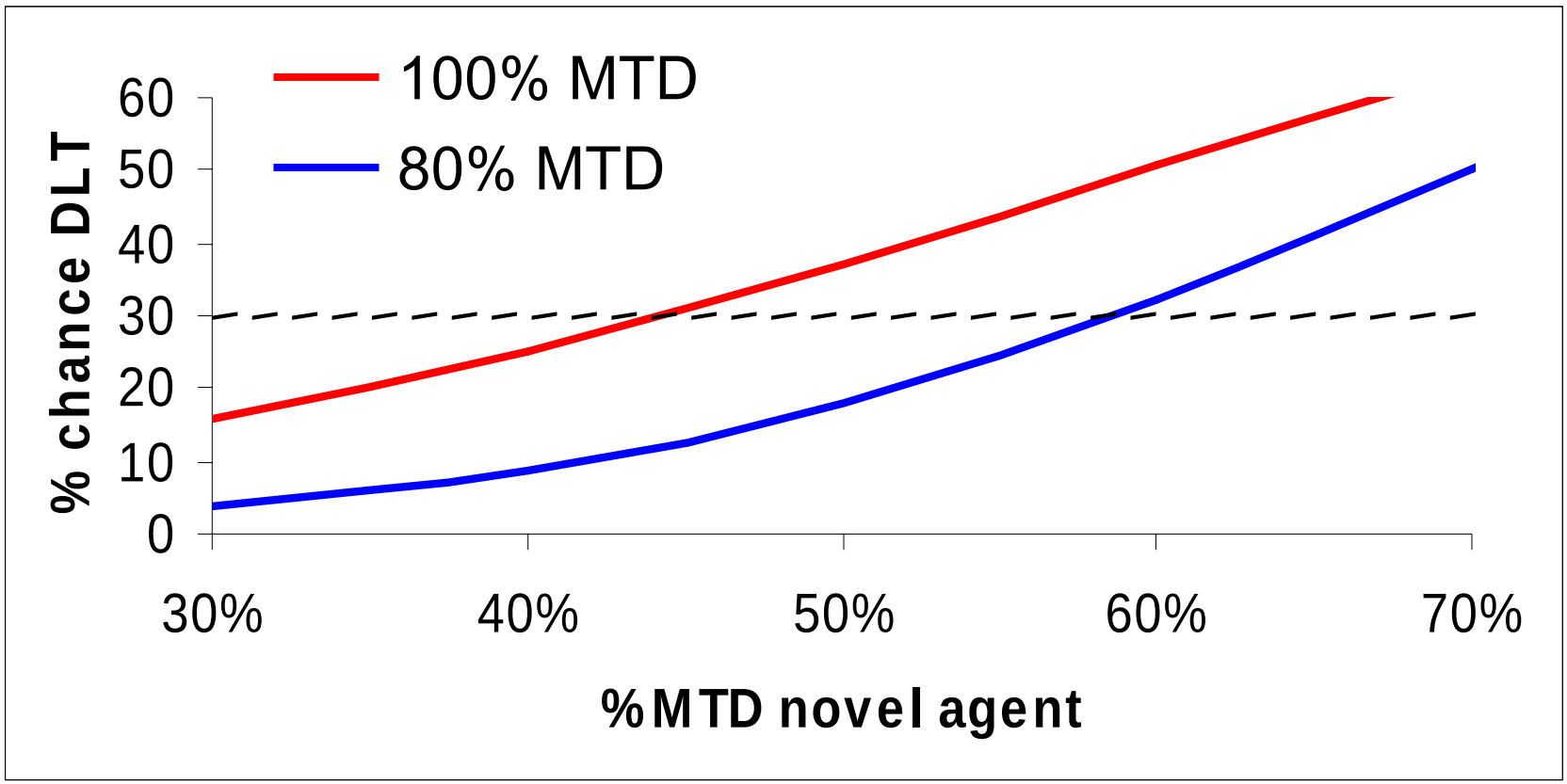
July 2001 - 26th April 2002

% MTD	30	40	50	60
80		0/3	0/3	
100				



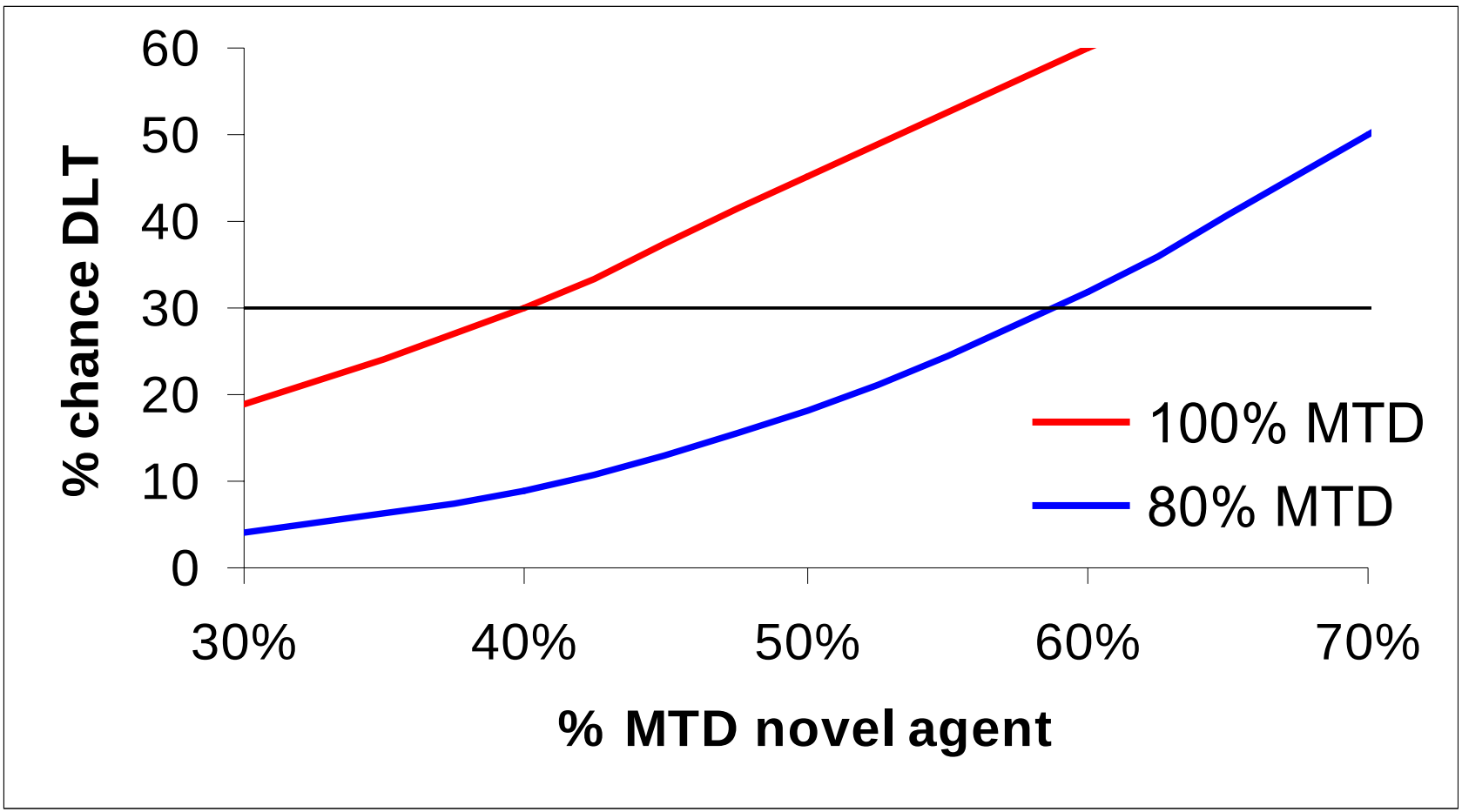
13th June 2002

% MTD	30	40	50	60
80		0/3	0/3	1/1
100	0/1			



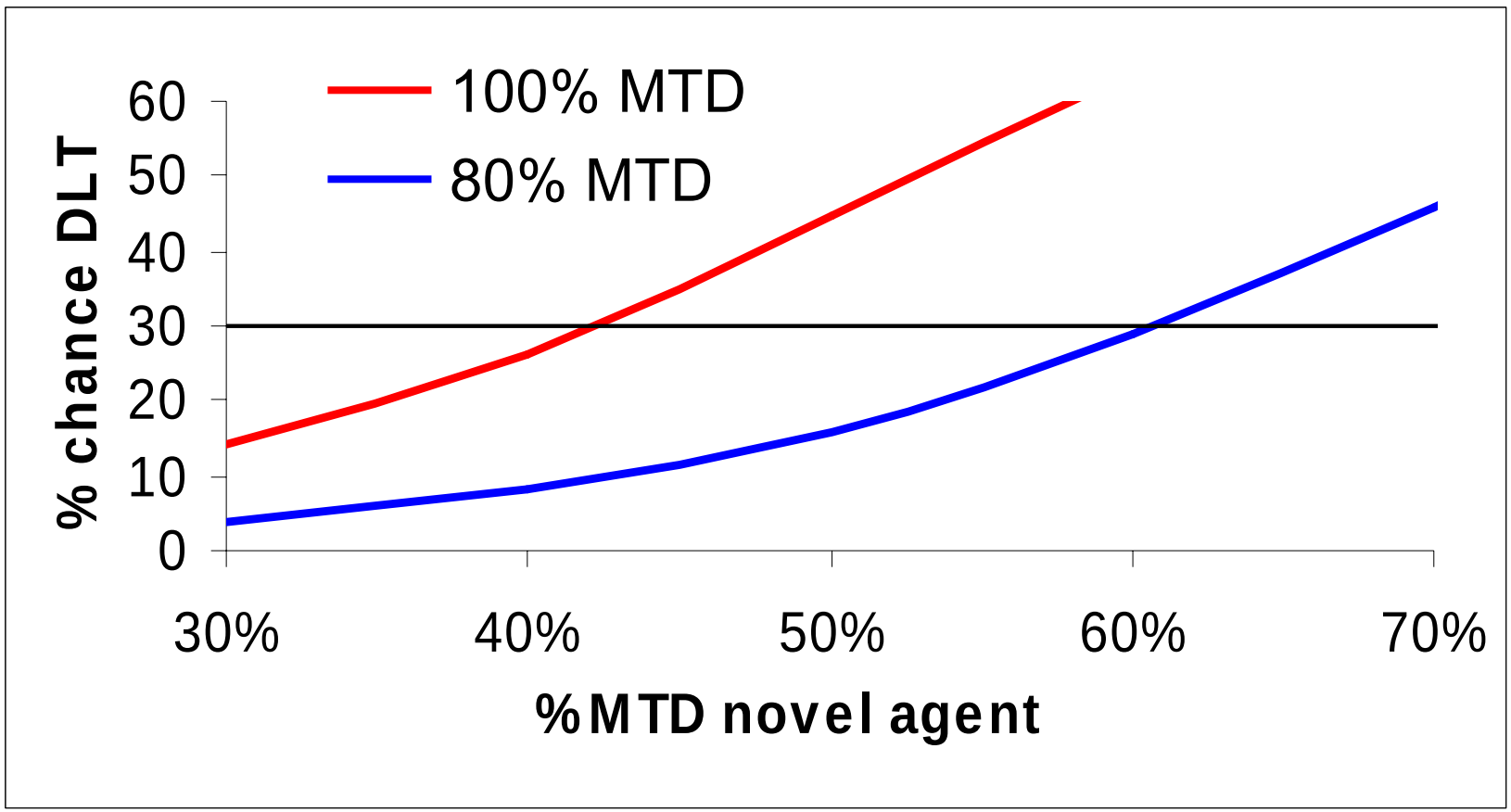
18th July 2002

% MTD	30	40	50	60
80		0/3	0/3	1/1
100	0/1	0/1	1/1	



23rd April 2003

% MTD	30	40	50	60
80		0/3	0/3	2/5
100	0/1	0/3	2/4	



Future directions

- Organ-system specific models are more useful - but always need “empirical insurance” in real-life drug development.
- Dimensions need not be dose.
- Phase I is pivotal for drug success, and it can be improved substantially.
- DLT is the most information-poor measure, even empirical categorical models would be a major improvement