Design of Controlled Clinical Trials

by

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Sample Size

- The probability of erroneously claiming difference between groups (Type I errors or significance level). {wanted as small as possible}
- The probability of detecting a real difference between groups. (Detection level or 1 Type II error). {wanted as large as possible}
- Clinical relevant difference. How large should a difference be in order to be of clinical interest?
- Optimalisation of study design.
- Degree of heterogeneity in the study population.
- Observation methodology.

Designs of CCT's

BETWEEN PATIENT DESIGNS

Parallel group design

Stratified design

Factorial designs

WITHIN PATIENT DESIGNS

Latin Square design

Semi cross- over design

Greaco Latin square design

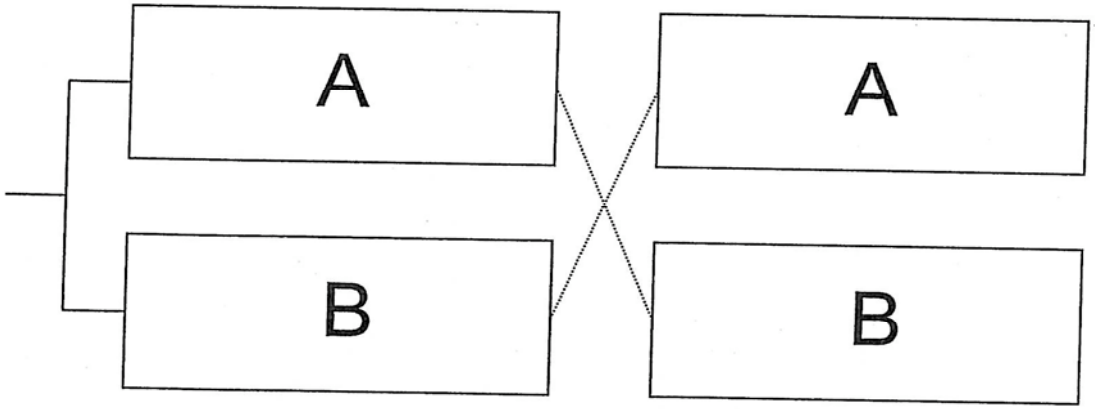
Multi-cross-over design

Between patient designs

- **Advantage**
  - Accepted by the authorities all over the world
  - Will always give information
- **Disadvantage**
  - Need a lot of patients
  - Might result in two or more groups which is not initially comparable
  - Predefined and standardized interventions and investigations

Cross-over design

The patients are equally allocated to one of two treatment sequences (A-B) or (B-A).



1. Registration period

"Wash-out"

2. Registration period

Greaco Latin Square Design

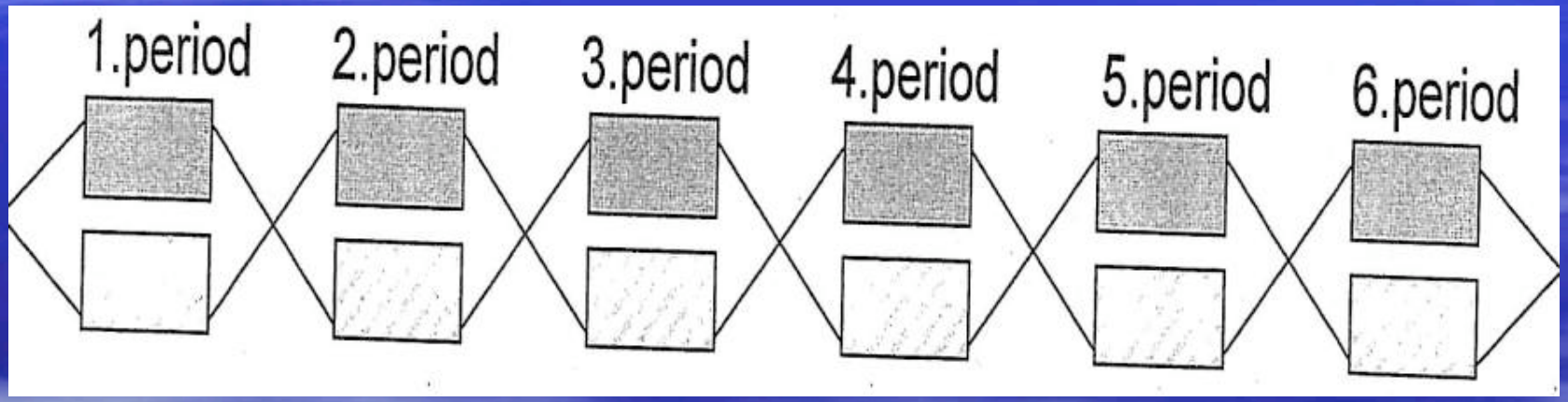
A-B-C

B-C-A

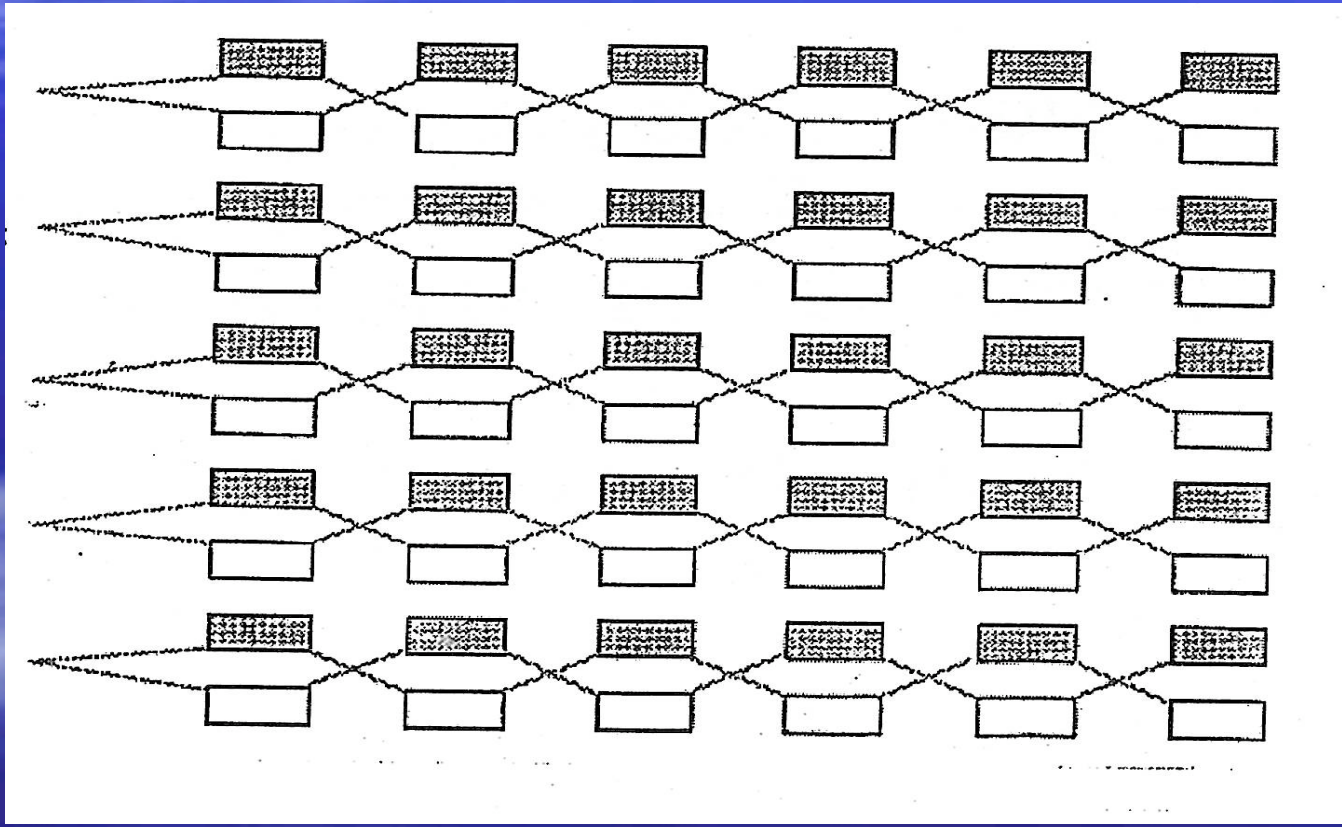
C-A-B

A-B-C	A-C-B
B-C-A	C-B-A
C-A-B	B-A-C

Multi cross over design



Combined MCO and Parallel group design



Within Patient Design

- **Advantage**

Reduces the needed number of patients

Able to discover small differences between interventions

- **Disadvantage**

The patient needs to be in the same condition at the start of every period

The number of patients in each group has to be absolutely the same.

The duration of the study might be too long

A wash-out period between each intervention sequence is needed

Predefined and standardized interventions and investigations

Designs of CCT's

Adaptive designs

Play-the-Winner design (PTW)

Modified Play-the Winner design (MPTW)

Randomized Play-the-Winner design (RPTW)

Weighted Play-the-Winner design (WPTW)

Sequential designs

Triangular finite and infinite

Trapezium finite and infinite

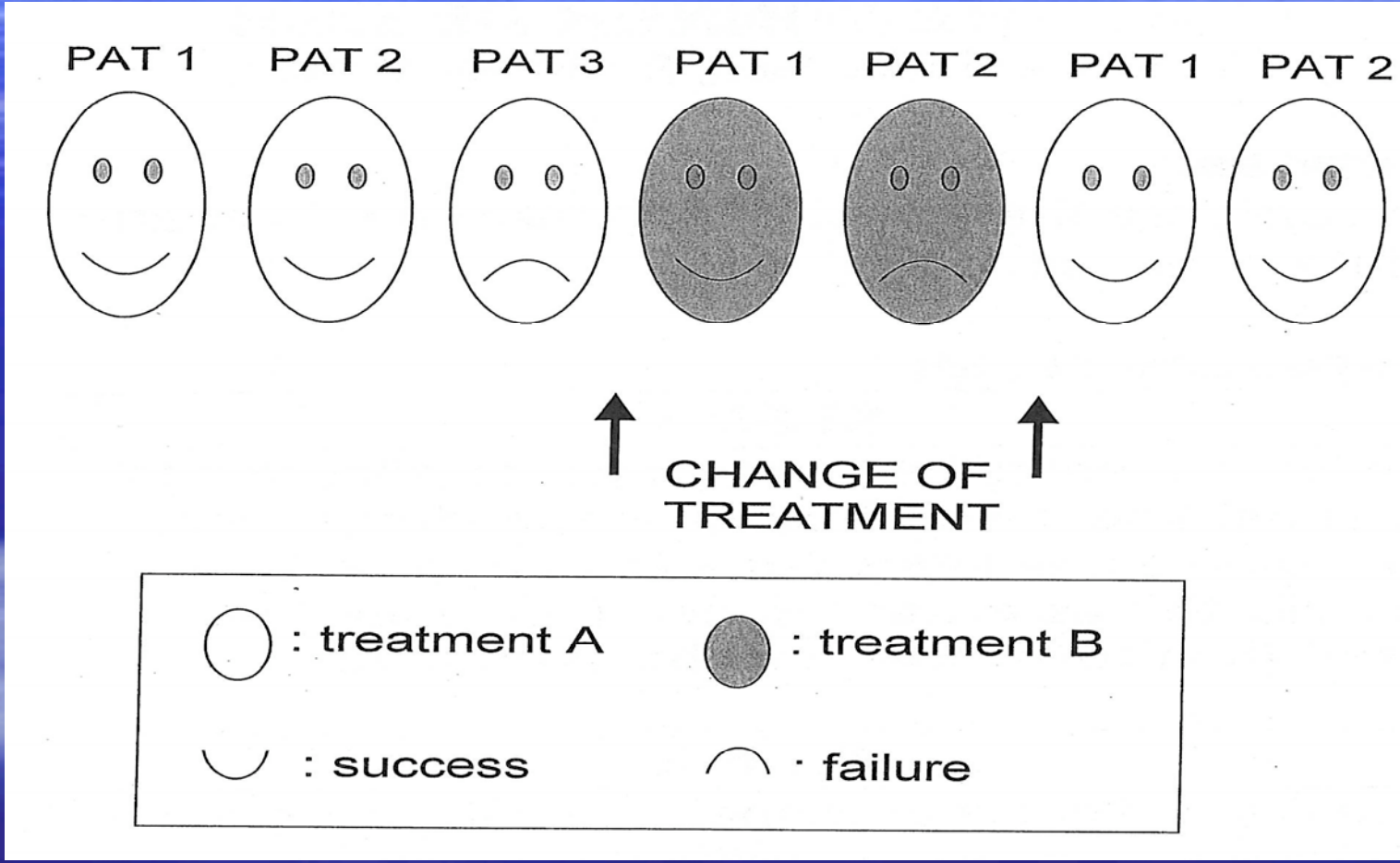
Response surface designs

Binomial plain design

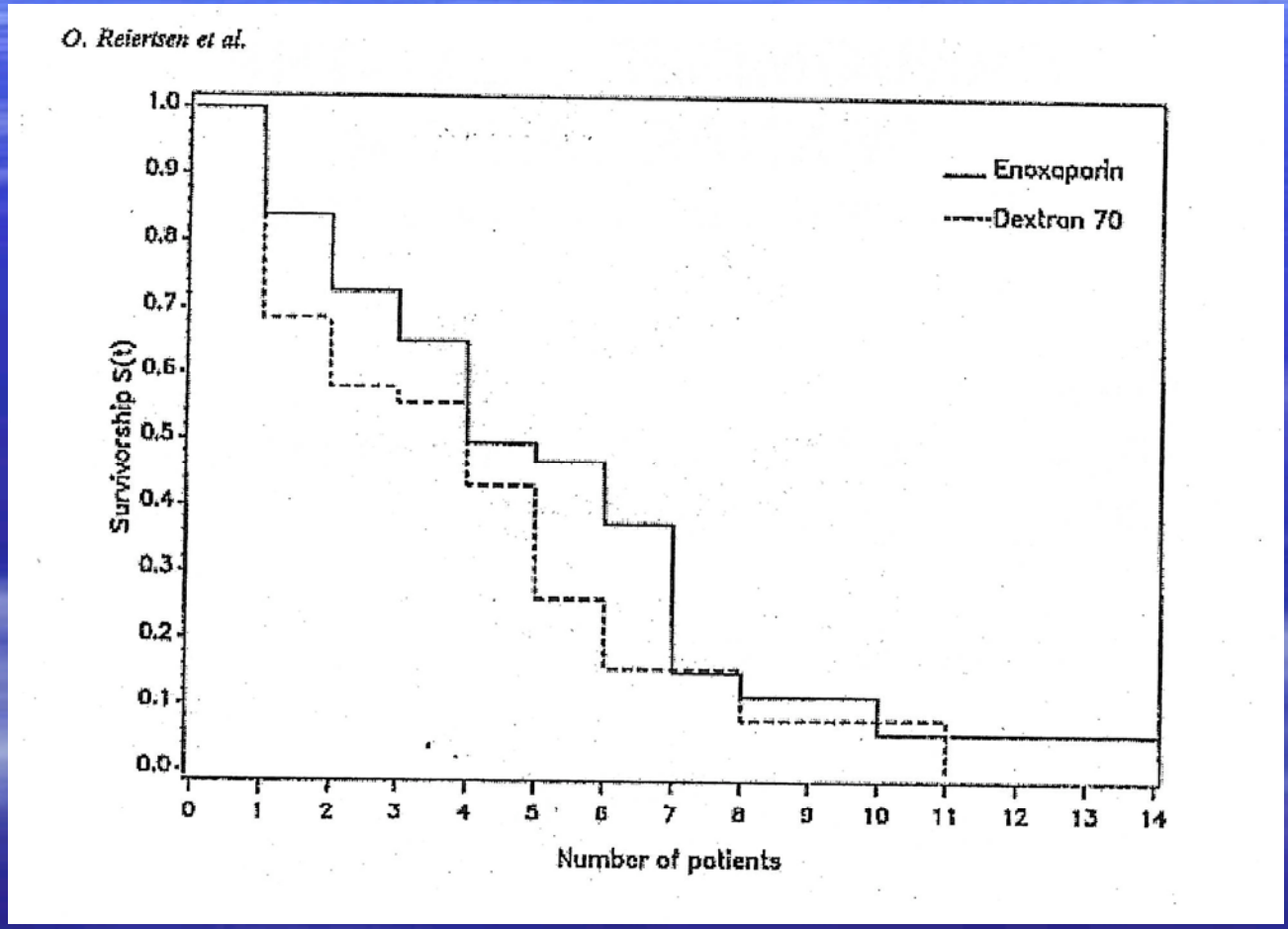
Iteration design (within patients)

Pathway design (between patients)

Play-the winner Design



Expression of the results from PTW

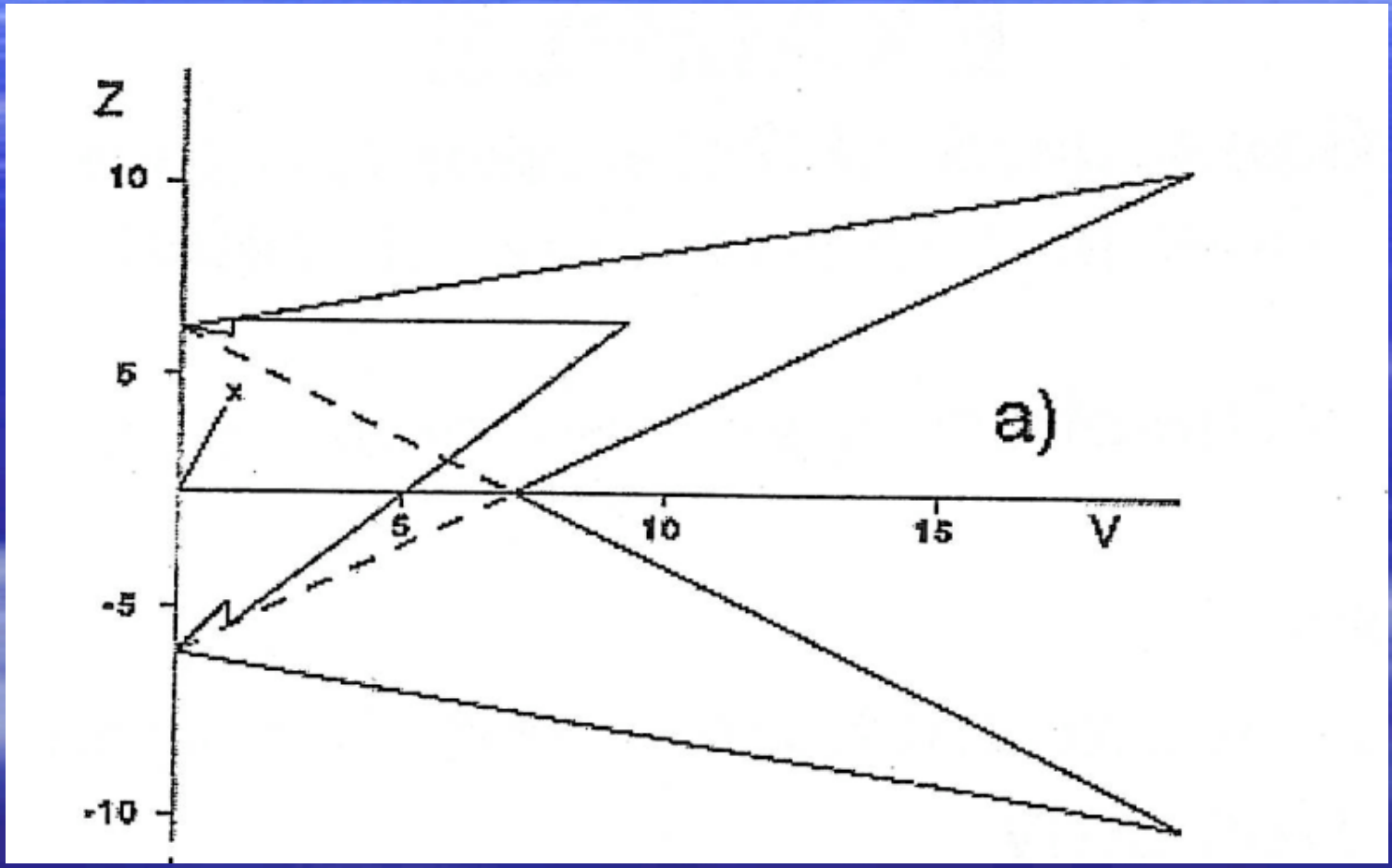


Adaptive Design

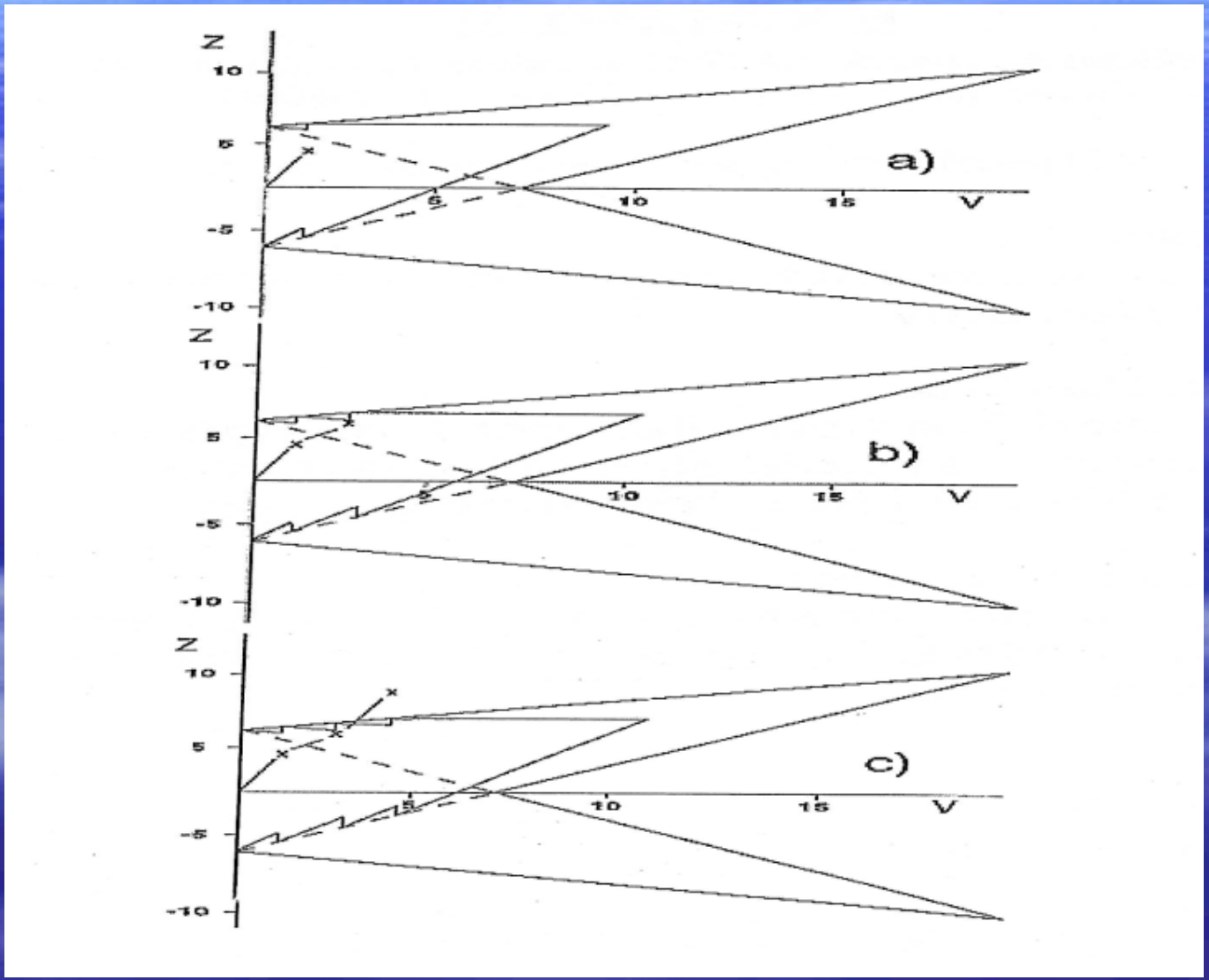
- **Advantage**
  - To be performed during the daily routine.
  - A controlling design, recording what happens in a real situation
  - The obtained study population will be close to the reference population
  - It is a family of design between Epidemiology and CCT

- **Disadvantage**
  - Needs a large sample size
  - Not commonly accepted as a randomised controlled design

Triangular finite Sequential Design



Example of sequential design



Sequential Designs

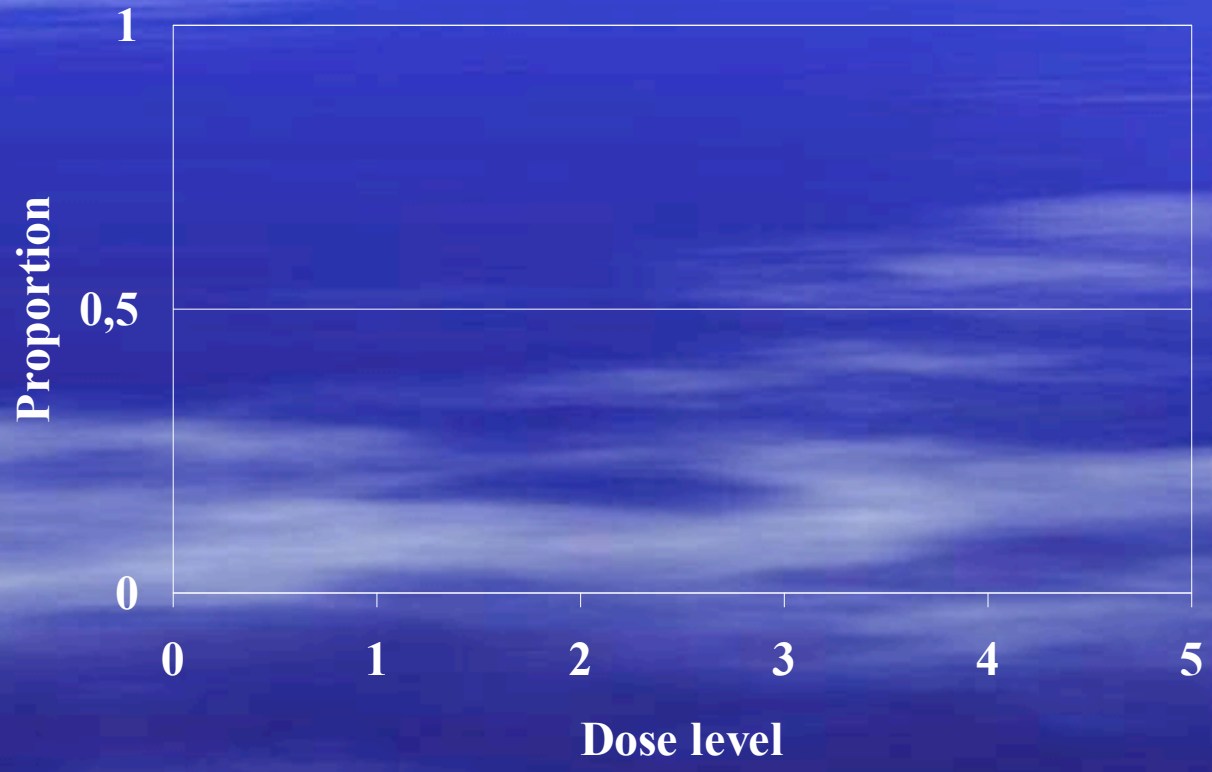
- **Advantage**
  - Reduces the needed number of patients
  - Discover during the trial if something unexpected or a dangerous situation occurs
  - Stops the trial when the aim can be answered
  - Can be combined with all kind of designs

- **Disadvantage**
  - Have to be statistically monitored during the study
  - Need special data software
  - Need more than a basic knowledge of statistics

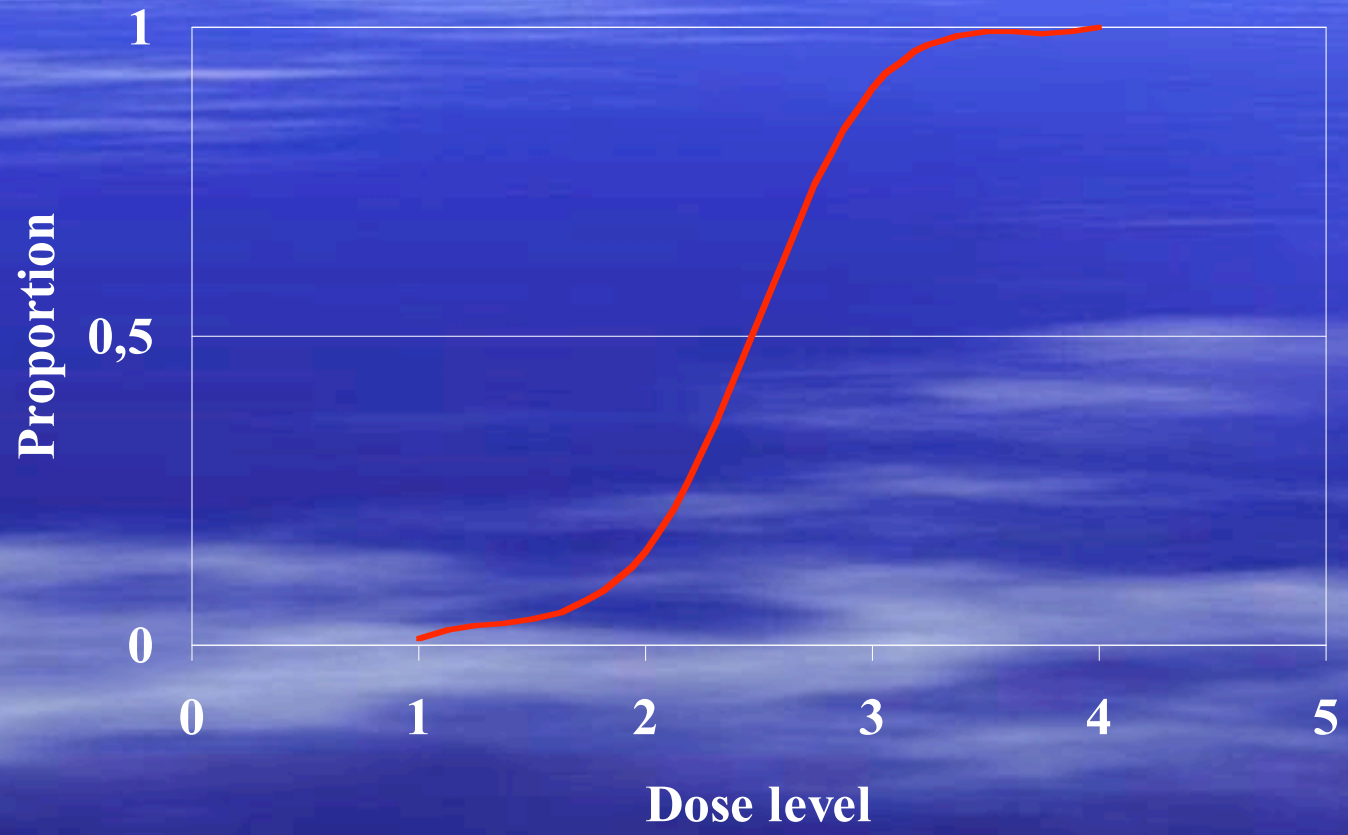
Response surface design

- **Advantage**
  - Can be used together with different other designs
  - Increase the information by a given number of laboratory animals
  - Reduce the number of laboratory animals without loss of information
  - The intervention is not prefixed but dependent on the results obtained at the last investigation
  - Makes the time for interventions and investigation stochastic

Selection of doses



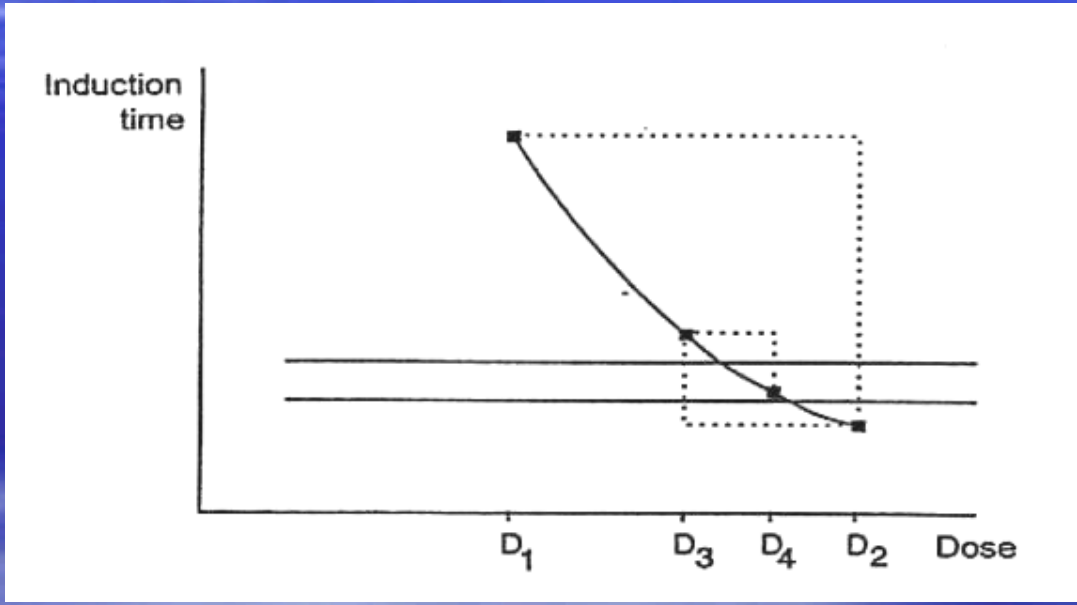
Selection of doses



Response surface design

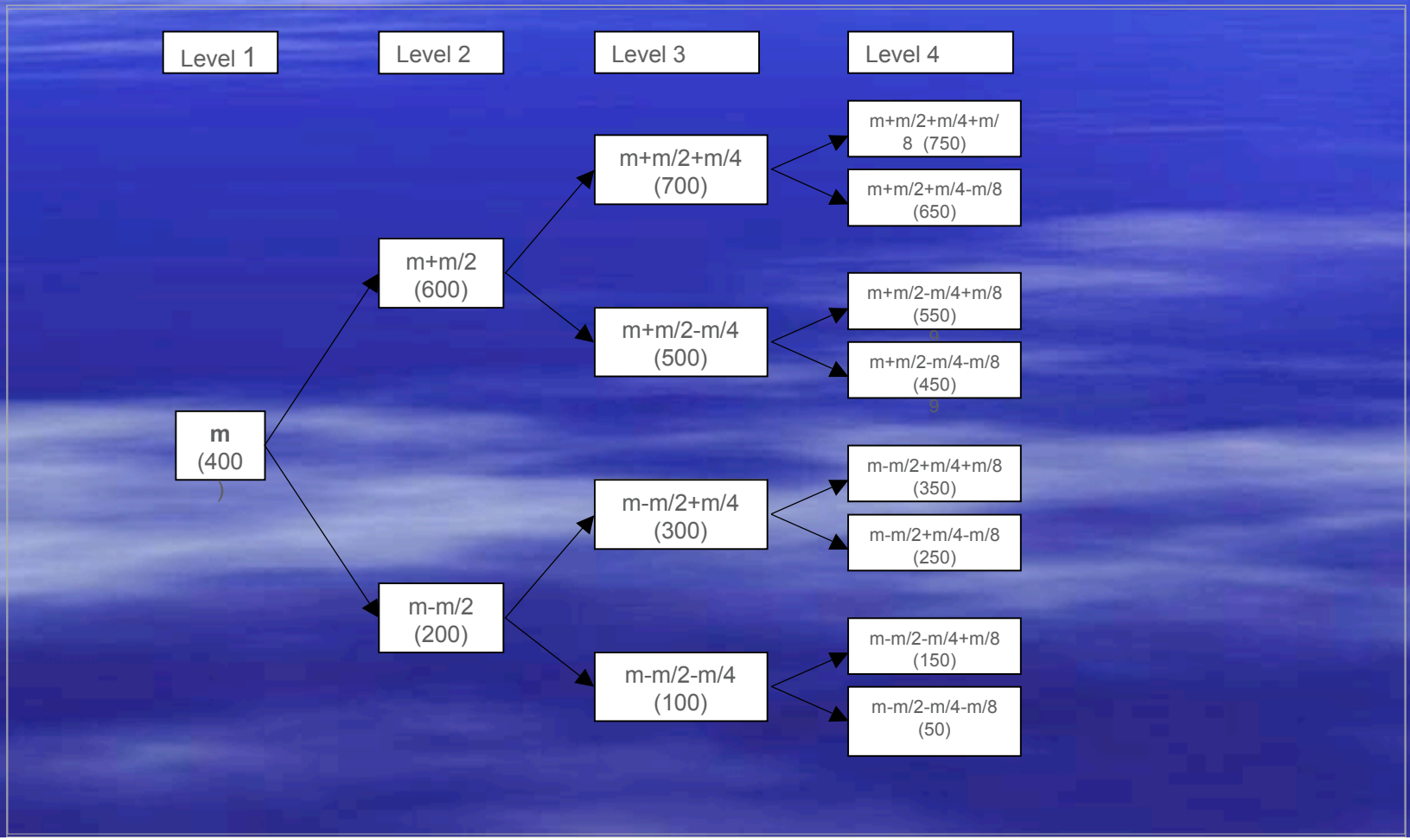
- Aim: Dose finding studies
  - and Controlled clinical studies
- Background situation
  - With some prior knowledge
  - Without or limited knowledge

Response surface design with iteration

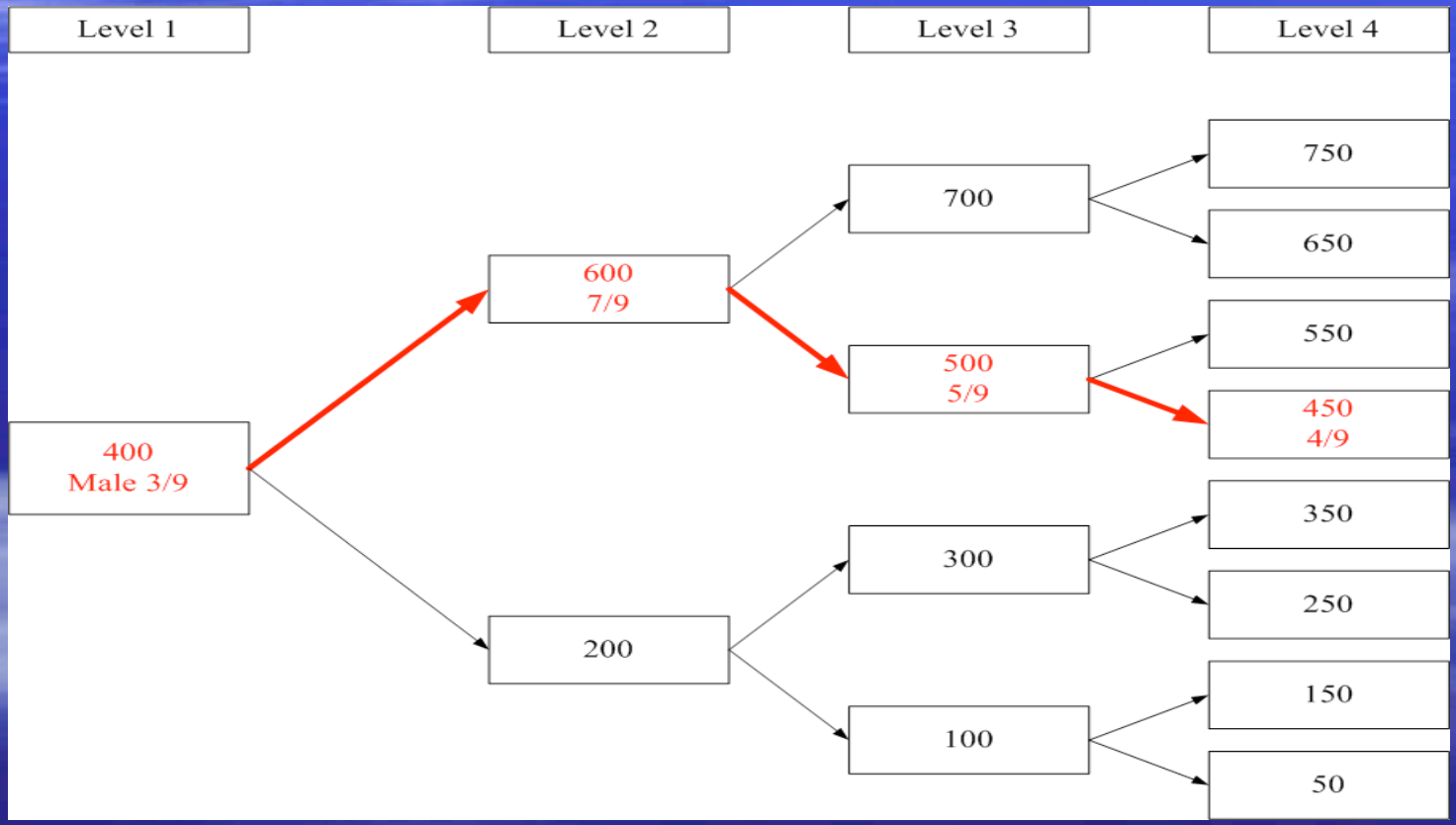


- In order to get similar power to that obtained by 16 animals in this design, 198 animals have to be included in a traditional design.

A general four level Response Surface Pathway Design



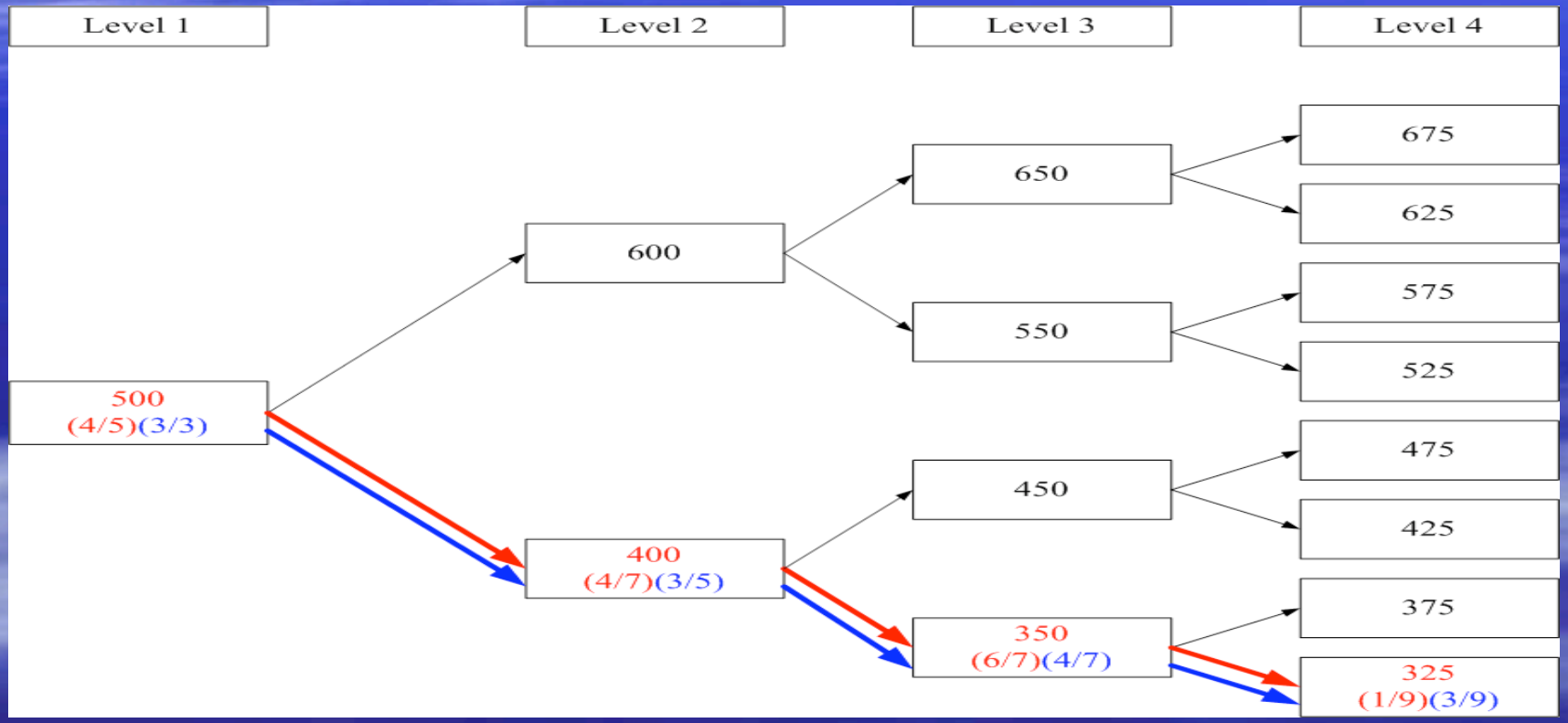
The response Pathway of Yessotoxin expressed with dose levels and proportion of dead mice



The proportion of dead mice with 95% confidence intervals at different dose levels in the two comparative designs.

Dose level (µg/kg.bw.)	Response surface design	Evenly distributed dose levels
	Proportion of dead mice	Proportion of dead mice
700		100,0 (66,4 – 100,0)
600	77,8 (40,0 – 97,2)	
500	55,6 (21,2 – 86,3)	55,6 (18,0 – 94,7)
450	44,4 (13,7 – 78,8)	
400	33,3 (7,5 – 70,1)	
300		0,0 (0,0 – 33,6)
100		0,0 (0,0 – 33,6)

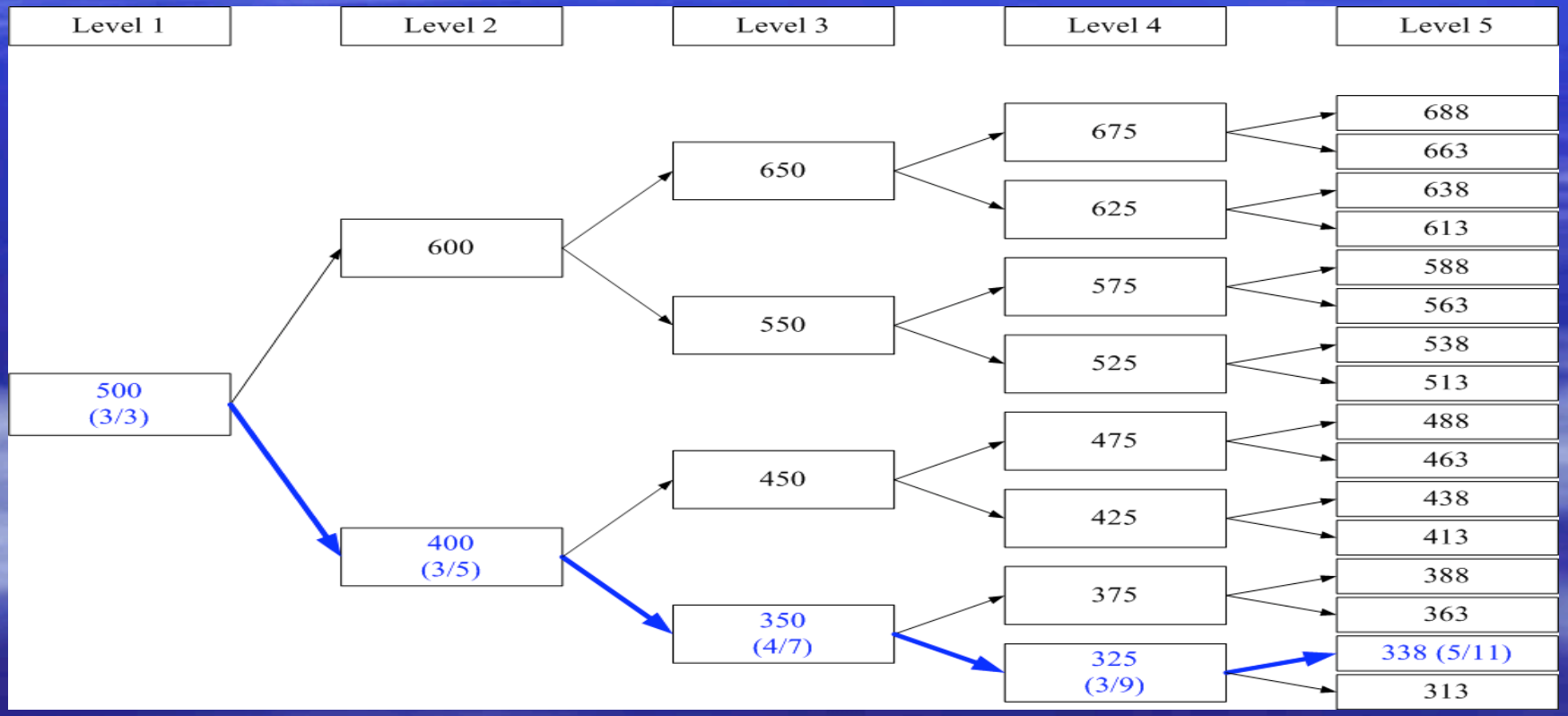
The response Pathway of DTX-2 with semi optimal (red) and optimal (blue) design expressed with doses and proportion of dead mice



The proportion of dead mice with 95% confidence intervals at different dose levels in the semi optimal and the optimal response surface pathway designs.

Dose level (µg/kg.bw)	Semi optimal design	Optimal design
	Proportion of dead mice	Proportion of dead mice
500	80,0 (28,4 – 99,5)	100,0 (29,2 – 100,0)
400	57,1 (18,4 – 90,1)	60,0 (14,7 – 94,7)
350	85,7 (42,1 – 99,6)	57,1 (18,4 – 90,1)
325	11,1 (0,3 – 48,3)	33,3 (7,5 – 70,1)

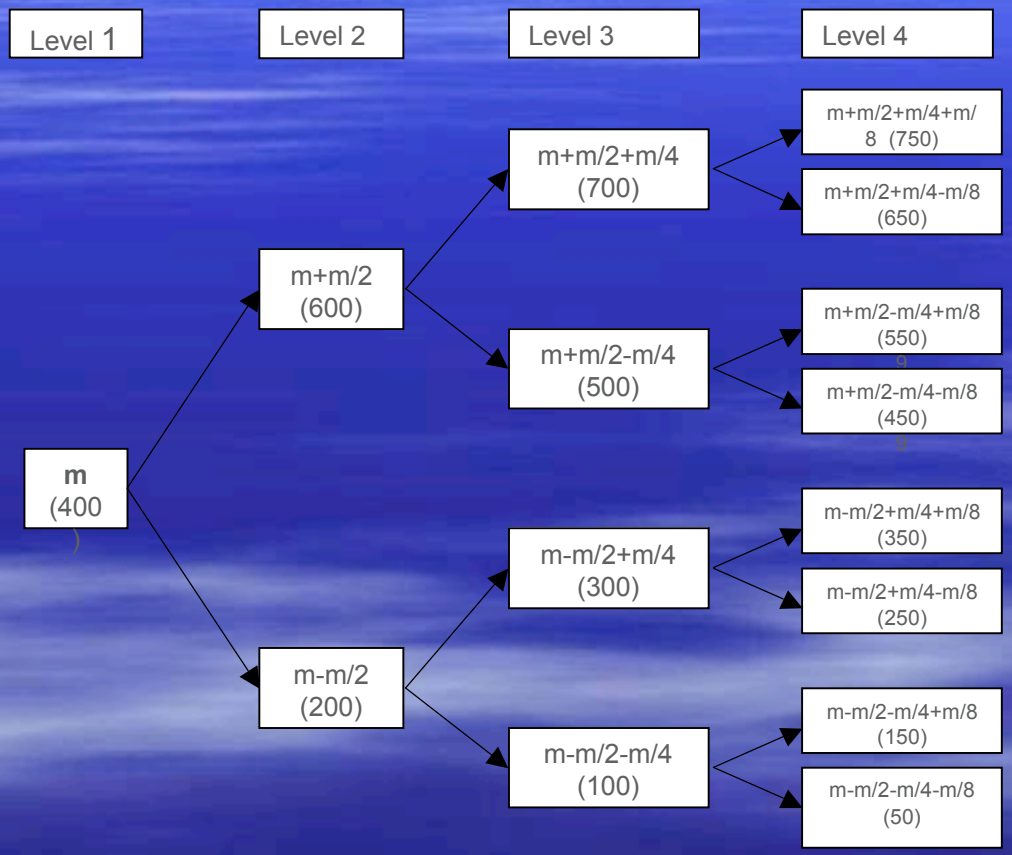
The five level response surface Pathway of DTX-2 with optimal design expressed with doses and proportion of dead mice



Comparison of results

Design	Dosed levels used (µg/kg bw	Number of dead mice	Number of mice used	Estimation of LD_{50} (µg/kg bw) with 95% confidence intervals in brackets
RSP_A-design (Semi optimal)	500	4	5	366 (316 – 424)
	400	4	7	
	350	6	7	
	325	1	9	
RSP_B-design (Optimal)	500	3	3	355 (301 – 419)
	400	3	5	
	350	4	7	
	325	3	9	
Level 5	338	5	11	353 (310 – 402)

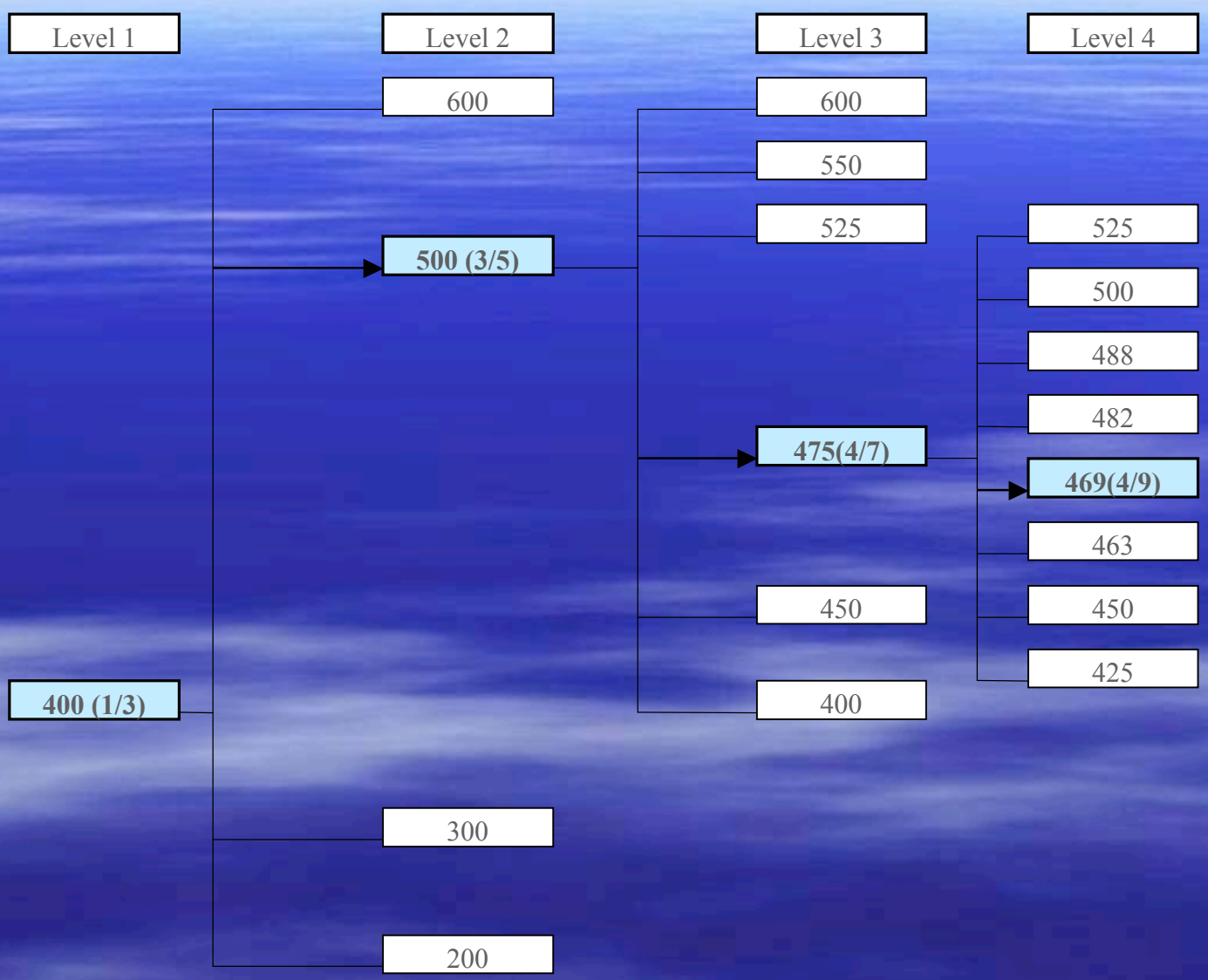
Basic change in dose levels



From Fixed to Stochastic observation time or dose levels

Number of dead mice	Level 2 (m_2)	Level 3 (m_3)	Level 4 (m_4)	Level 5 (m_5)
0	$m_1 + m_1/k$	$m_2 + m_1/k^2$	$m_3 + m_1/k^3$	$m_4 + m_1/k^4$
1	$m_1 + m_1/k^2$	$m_2 + m_1/k^3$	$m_3 + m_1/k^4$	$m_4 + m_1/k^5$
2	$m_1 - m_1/k^2$	$m_2 + m_1/k^4$	$m_3 + m_1/k^5$	$m_4 + m_1/k^6$
3	$m_1 - m_1/k$	$m_2 - m_1/k^4$	$m_3 + m_1/k^6$	$m_4 + m_1/k^7$
4		$m_2 - m_1/k^3$	$m_3 - m_1/k^6$	$m_4 + m_1/k^8$
5		$m_2 - m_1/k^2$	$m_3 - m_1/k^5$	$m_4 - m_1/k^8$
6			$m_3 - m_1/k^4$	$m_4 - m_1/k^7$
7			$m_3 - m_1/k^3$	$m_4 - m_1/k^6$
8				$m_4 - m_1/k^5$
9				$m_4 - m_1/k^4$

RSP design with stochastic interventions



Comparison of fixed and stochastic dose steps

Design	Dosed levels used (µg/kg bw)	Number of dead mice	Number of mice used	Estimation of LD_{50} (µg/kg bw) with 95% confidence intervals in brackets
Four level RSP-design using a minimum number of mice and pre-fixed doses	**400**	1	3	446 (345 – 577)
	450	5	9	
	500	4	7	
	600	4	5	
Four level RSP-design using a minimum number of mice and result-related doses	**400**	1	3	468 (389 – 563)
	469	4	9	
	475	4	7	
	500	3	5	

Conclusions

The use of Response Surface Pathway design in CCT and Laboratory Animal Research will:

1. Increase the information from a given number of animals
2. Reduce the number of animals without loss of information to 1/3
3. In order to optimize the design, the number of animals has to be reduced to a minimum at the first design level