Biostatistics 752: Clinical Trials

THE UNIVERSITY
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at CHAPEL HILL

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Chapter 2
Dose-Finding Clinical Trials
Part 1

Phase 1 clinical trials

- **First study of a new drug in humans**
- Conducted under an **IND** or **IDE** (Investigational Device Exemption) (US FDA requirement)
- Two types of phase 1 trials
  - **Life-threatening diseases (e.g., oncology, AIDS): patients are studied**
  - **Non-life-threatening diseases (e.g., allergies, pain): healthy volunteers are studied**
- Objectives
  - To determine pharmacokinetic and pharmacodynamic properties
  - To find a range of well-tolerated doses in humans
  - To find the maximum tolerated dose (MTD)
- Trial setting is often a phase 1 clinic - dedicated facility with beds, local lab
- Inpatient stays (e.g., 24-48 hours) required for continuous monitoring of blood levels (IV)

Phase 1 in non-life-threatening diseases : why not patients?

- No clinical experience on product is available
- Trial often involves intensive study procedures—burden may be too great for severely diseased patients
- Potential confounding of adverse reactions with disease or concomitant medications
- May be difficult to recruit patients—no evidence of benefit yet
- Extremely low risk of serious adverse events in Phase 1 trials justifies participation of healthy volunteers
- Subjects are often male (to avoid child-bearing potential), aged 18-35; non-smoking; disease free; no concomitant medications, etc.
  - "Normal" (FDA) subjects are free from abnormalities which would complicate the study interpretation or increase the sensitivity of the subject to toxic potential of drug

Phase 1 trials: non-life threatening diseases

- **Most phase 1 studies are placebo controlled**
  - Placebo group is included to reduce observer bias
  - May enable comparison of the active drug with placebo
- **More than half of phase 1 studies are double blind**
- Usually 3-8 dose levels are investigated
- *Parallel single dose design*-- a single dose is administered once to each subject
- *Parallel multiple dose design*--multiple administrations of the same dose are given to each subject

Ref: Buoen et al., 2005

Choice of dose levels

- Very often the starting dose is 1/10 of the dose (adjusted for height or weight) that causes 10% mortality in pre-clinical testing in animals (e.g., rodents)
  - Starting dose D = **1/10 of LD_{10}**
- How to increase?
  - Increments
    - Arithmetic: D, 2D, 3D, 4D, … (toxic drugs)
    - Geometric: D, 2D, 4D, 8D, 16D, … (usual)
    - Fibonacci: D, 2D, 3D, 5D, 8D, 13D, … (oncology)
    - Modified Fibonacci: D, 2D, 3.3D, 5D, 7D, 9D, … (oncology)

Leonard Pisano Fibonacci
born 1170 in Pisa; died 1250

- A pair of rabbits are placed in a pen. How many pairs of rabbits can be produced in a year, if it is supposed that every month each pair begets a new pair which from the second month on becomes productive?
- The resulting sequence is 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, …, a sequence in which each number is the sum of the two preceding numbers
- **The ratio of successive terms approaches $(\sqrt{5}-1)/2 = 0.61803$ …the so-called golden ratio (or golden section) $1/0.61803 = 1.61803$**

Fibonacci and modified Fibonacci dosing

Step	Fibonacci Dose	Modified Fibonacci	% Increment
1	D	D	--
2	2 x D	2 x D	100
3	3 x D	3.3 x D	67
4	5 x D	5 x D	50
5	8 x D	7 x D	40
6	13 x D	9 x D	29
7	21 x D	12 x D	**33**
8	34 x D	16 x D	**33**

D represents the starting dose and is selected based on pre-clinical information, e.g. 1/10 of LD_{10}

Designs for phase 1 studies in non-life-threatening diseases

Dose	**0**	**1**	**2**	**3**	**4**
Cohort 1	2	6	0	0	0
Cohort 2	2	0	6	0	0
Cohort 3	2	0	0	6	0
Cohort 4	2	0	0	0	6
Cohort 5 (Extension)	2	2	2	2	2

Designs for phase 1 studies in non-life-threatening diseases

- Most commonly used design:
  - Dose escalation across cohorts
  - Number of cohorts (k) = number of active doses (n)
  - Each cohort contains m patients
  - Subjects in cohort i receive either placebo or dose i only
  - Number of placebo patients is usually chosen for overall balance across doses

TeGenero phase 1 Trial, 2006

At 8 o'clock on the chilly morning of Monday 13 March 2006, 8 healthy young men were injected as part of a phase 1 trial. The volunteers were all paid for their participation. Within minutes six of them were reportedly writhing in pain, tearing at their clothes, screaming and retching. The two others waited in terror for their turn, but they were in luck: they had been given placebo and escaped.

All 6 men, reportedly suffering from multiple organ failure, were transferred from the clinical trials unit run by the US-based company Parexel at Northwick Park Hospital in London to the hospital's intensive care unit. There were fears that at least two of the men would die.

TeGenero phase 1 trial: what went wrong?

Six volunteers took the drug TGN1412, a candidate for autoimmune and inflammatory diseases manufactured by German company TeGenero.

TGN1412 itself had been given to “non-human primates”, which TeGenero argued would be a good animal model for testing safety and efficacy. TeGenero had initially claimed that no adverse events were detected in animal trials, but later amended that to say that monkeys had experienced swollen glands. Contrary to the assumption made by TeGenero, TGN1412 does not act in monkeys in the way it does in humans, and the non-human primate was therefore not a good model.

TGN1412 is that it acts on the immune system. The immune system differs from species to species more than other systems. What is more, unlike many other monoclonal antibody drugs whose function is to reduce or suppress the immune response, TGN1412 is designed to stimulate it. It also opens the possibility of a runaway effect, which is almost certainly what happened.

TeGenero phase 1 trial: what went wrong?

Volunteer ID	Randomized group TG = TGN1412	Time of intravenous administration	Time after dosing to care transfer
A	TG 8.4 mg	08.00	16 h
B	Placebo	08.10	
C	TG 6.8 mg	08.20	15 h 30 min
D	TG 8.8 mg	08.30	16 h
E	TG 8.2 mg	08.40	12 h
F	TG 7.2 mg	08.50	16 h
G	TG 8.2 mg	09.00	16 h
H	Placebo	09.10	

Table 1 from Senn et al. (2007)

TeGenero phase 1 trial: what went wrong?

It is usual practice to try the drug on a single individual first, and not to give it to others until it seems safe to do so. That does not appear to have been the case in the TGN1412 trials, which is why all six volunteers suffered the violent reactions.

The notoriety of the case has caused British officials to review how experimental drugs are tested in humans.

Abandoned by investors in the wake of a catastrophic phase 1 trial, TeGenero filed for bankruptcy.

Bevacizumab, Rituximab, Cetuximab

Te Genero phase 1 trial, 2006

from http://www.i-sis.org.uk/PMOTTD.php

The health correspondent of the newspaper *Scotland on Sunday* asked the Medicines and Healthcare products Regulatory Agency (MHRA), and was told that since 2001 there have been 2,088 volunteers who have needed hospital treatment as a result of drug testing. In 2005 alone, there were 359 people in the UK who suffered what are called "suspected unexpected serious adverse reactions" (SUSARs). Now there are about 3,000 drug trials a year in the UK, and most SUSARs are nowhere near as serious as those experienced in the TGN1412 trial.

Adverse Events (AEs) graded by intensity:

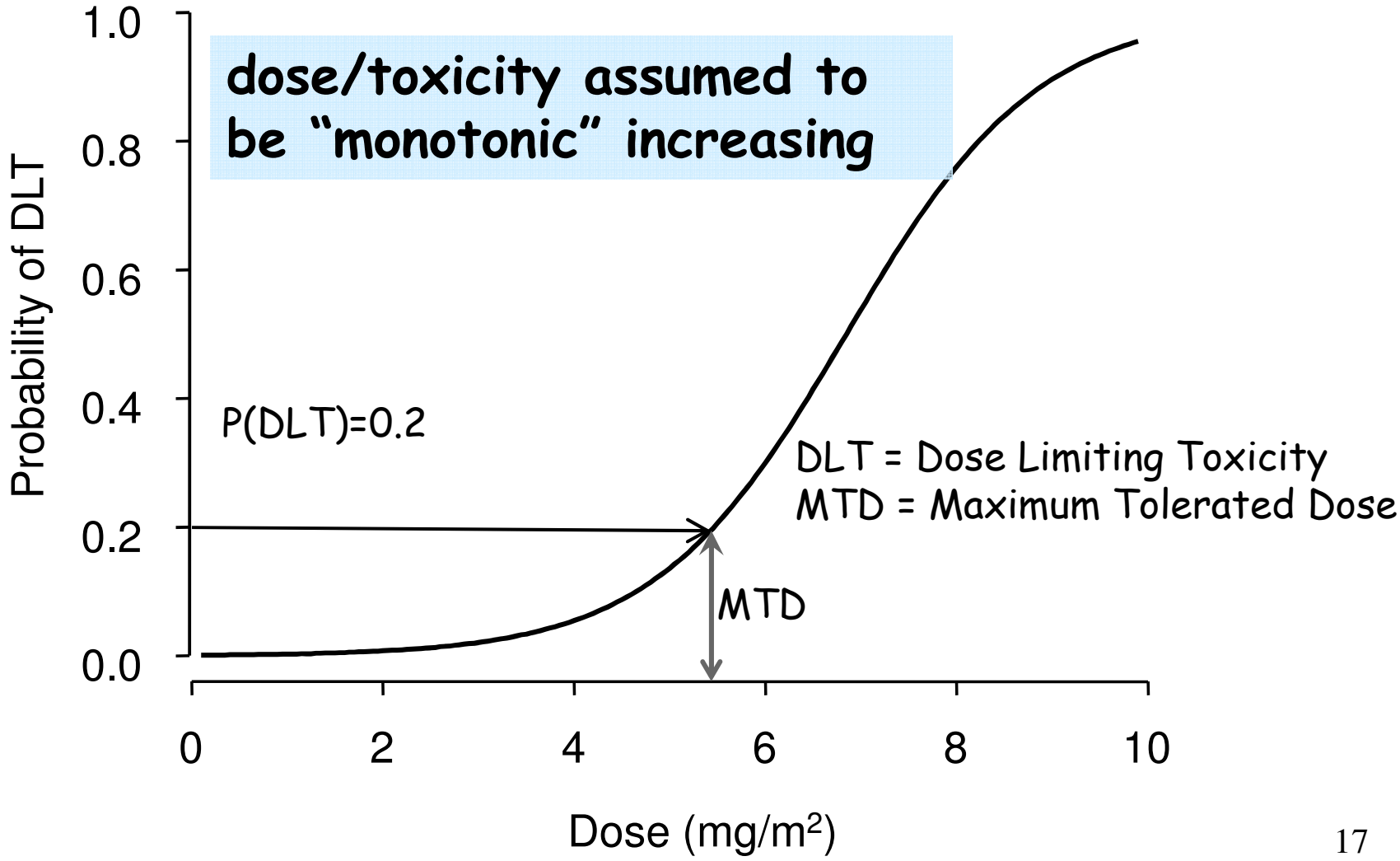
Mild, Moderate, Severe, Life-threatening, Death

Serious adverse event is an event which investigators judge to represent significant hazards

Biotrial's phase 1 study, 2016

- The trial recruited 128 healthy volunteers aged 18–55, who were paid €1,900 (US$2,060) each.
- Ninety people received different doses of the drug, and the remainder a placebo.
- The trial had tested escalating single doses of the drug without observing any serious adverse side effects.
- The six participants who fell ill were the first to receive repeat higher doses over the course of several days.
- The first participant to fall ill experienced adverse symptoms on 10 January and died on 17 January.
- Biotrial halted the trial on 11 January; the other five affected people were hospitalized in the days that followed.

Phase 1 trials in oncology



Phase 1 trials in oncology

In oncology, adverse events are referred to as toxicities

Toxicity or Dose Limiting Toxicity (DLT) or adverse event indicator is binary (YES or NO)

The target dose is the dose such that

$$\text{Probability}\{\text{toxicity at the target dose}\} = \Gamma,$$

where Γ is the target toxicity probability. In oncology, this dose is often referred to as the maximum tolerable dose (MTD).

For example $\Gamma = 0.2$ implies 20% of the subjects experience toxicity at this dose.

The toxicity probability is assumed to be a non-decreasing function of dose.

Why do we need to find the MTD?

- Usually, the therapeutic effect of a drug is believed to increase with dose.
- The dose of a study drug that a subject can receive is often limited by toxicity.
- Therefore the target dose is the maximum dose that is tolerable.
- In oncology the MTD is often investigated in a phase 2 trial.
- In non-life-threatening diseases the equivalent of the MTD is the highest dose in the range of doses that are investigated.

Phase 1 trials in Oncology

- Phase 1 trials in oncology treat patients since drugs are usually toxic.

- Do not want to treat many patients at either low, ineffective doses or at high, excessively toxic doses.

- Ethical considerations require to treat patients at lower doses before administering higher doses.

Therefore need to use adaptive design.

Examples of phase 1 trials

Example 1, non-oncology. New compound for treating memory and cognitive disturbances, might offer benefit to Alzheimer's patients.

Possible adverse events

Psychic: concentration difficulties
sleepiness/sedation
failing memory
depression
increased dream activity etc

Neurological: tremor, epileptic seizures etc

Example 2, oncology. New agent for graft versus host disease prophylaxis in patients undergoing stem cell transplantation.

Possible adverse events: veno-occlusive disease of the liver
pulmonary fibrosis
neurotoxicity

How to find the MTD?

WHAT ARE POSSBILE SUBJECT ALLOCATION STRATEGIES TO ESTIMATE THE MTD?

One possible allocation:

Parallel assignment of subjects with equal number of subjects at each dose

For example, 6 subjects at each of 6 doses for the total of 36 subjects

What are potential shortcomings of the parallel design with equal allocation?

- If adverse events can be severe it is **not ethical** to assign many subjects to doses higher than the MTD.

- The solution is to use **the escalating dose cohorts design or the escalation design**:

  Assign 6 subjects to dose 1

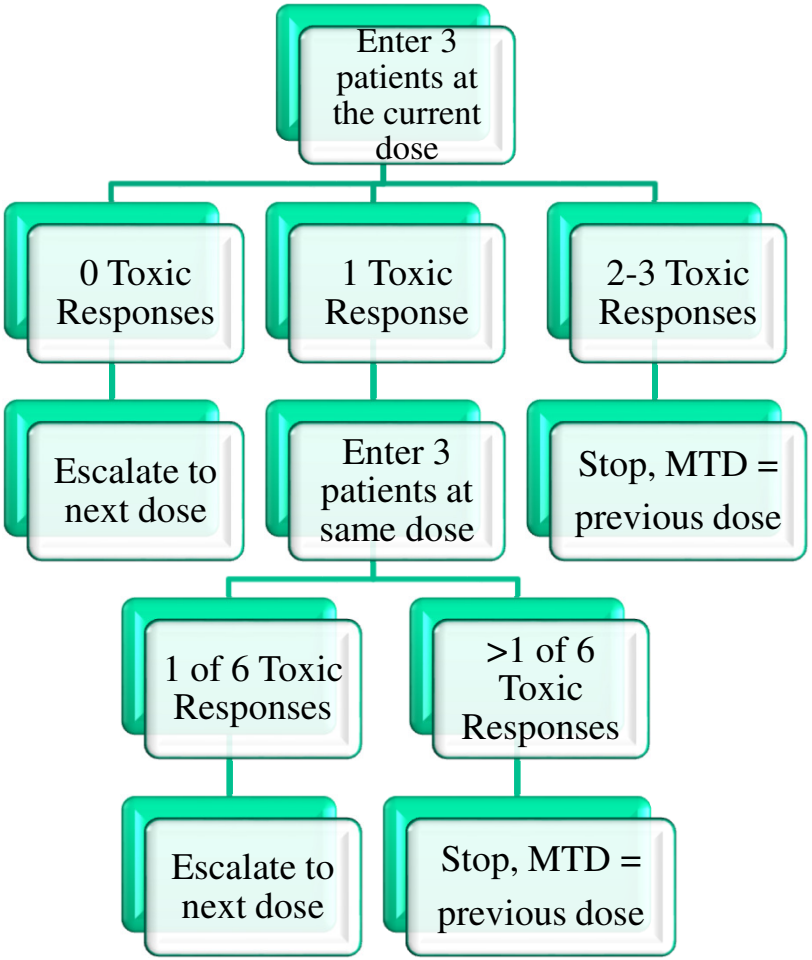
  - If toxicity proportion is < 0.2 (≤ 1 toxicities in 6 subjects), assign 6 new subjects to dose 2
  - If toxicity proportion is ≥ 0.2 (≥ 2 toxicities in 6 subjects), STOP
  - Continue until stopping point is reached

- The estimated MTD is the highest dose with estimated toxicity probability less than 0.2.

What are potential shortcomings of the escalation design?

- If adverse events are severe it is **not ethical** to assign **6 subjects** to a dose at once.
- A solution is to use a **3+3 design**
- The Traditional or Standard or 3+3 design is often used in Phase 1 studies in oncology.
- Patients are assigned in cohorts of 3 starting with the lowest dose.

Traditional or 3 + 3 design



If previous dose has only 3 patients, assign 3 more patients to that dose

If previous dose has only 3 patients, assign 3 more patients to that dose

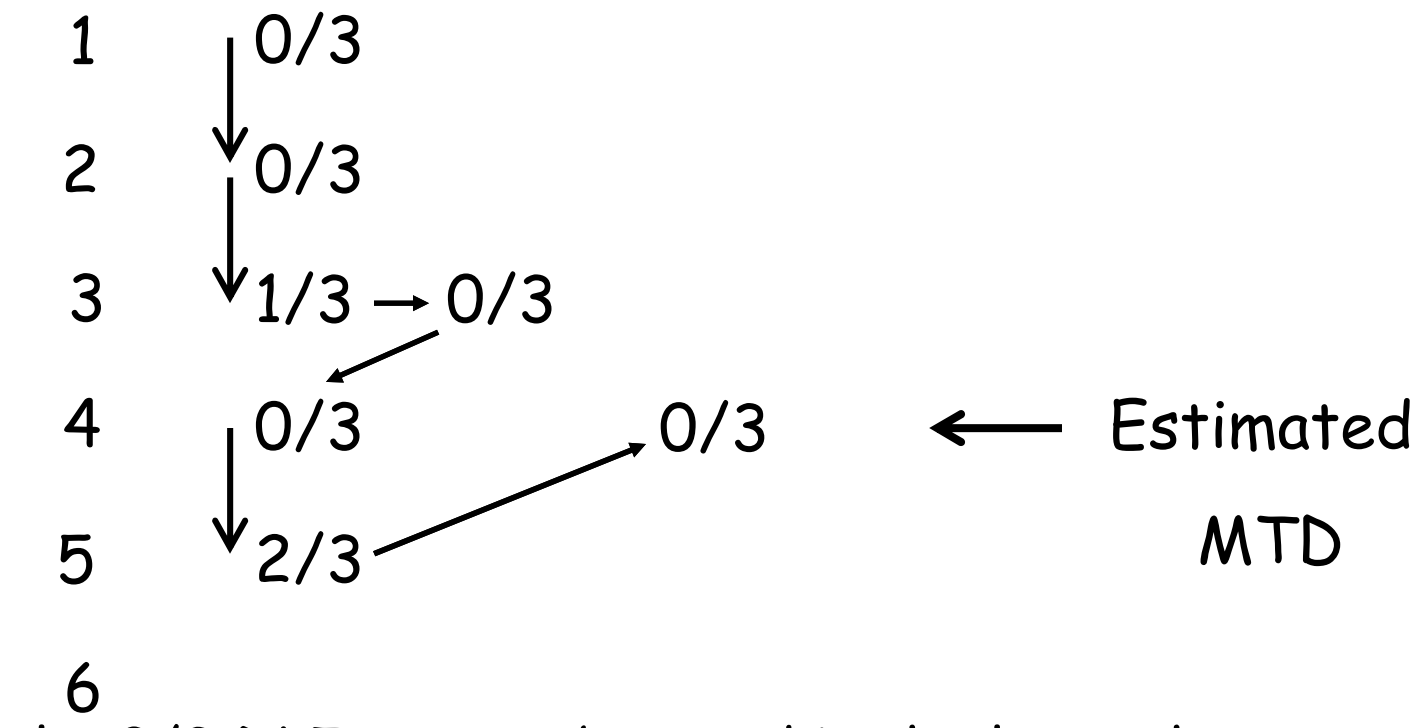
Traditional or 3+3 design

- If 0/3 DLTs, assign 3 new patients to the next higher dose
- If 1/3 DLTs, assign 3 new patients at this dose
  - if 1/6 DLTs, assign 3 new patients to the next higher dose
  - if ≥2/6 DLTs, STOP
- If 2/3 DLTs, STOP and assign 3 new patients to the preceding dose level unless there are already 6 patients at that level

- The estimated MTD is the highest dose level with observed toxicity proportion less than 0.33.

Example of the 3+3 design

Estimated MTD – highest dose with observed DLT proportion < 33%



If, for example, 2/3 DLTs were observed in the last cohort at level 4, the estimated MTD would have been level 3

Traditional or 3+3 design: operating characteristics

The frequency of stopping escalation at a certain dose level in the 3+3 design depends on toxicity probability at that dose as well as probabilities at all the lower dose levels.

The operating characteristics of the 3+3 design have been studied for a number of dose-toxicity scenarios by exact computations and simulations (Reiner et al. 1999; Lin and Shih, 2001; Kang and Ahn, 2001, 2002).

On average, the dose chosen by the 3+3 design as the MTD has the probability of toxicity of about

$$\Gamma \approx 0.2$$

Traditional or 3+3 design: operating characteristics

For example, if the doses are 100, 200, 330, 500, 700, 900 mg and the true DLT probabilities at these doses are 0.01, 0.05, 0.10, 0.20, 0.35, 0.50 respectively:

If one runs, say, 10,000 hypothetical trials with 3+3 design
3% of the trials will result in declaring 100 mg as the MTD;
10% of the trials will result in declaring 200 mg as the MTD;
25% of the trials will result in declaring 330 mg as the MTD;
38% of the trials will result in declaring 500 mg as the MTD;
20% of the trials will result in declaring 700 mg as the MTD;
4% of the trials will result in declaring 900 mg as the MTD.

Traditional or 3+3 design: advantages and disadvantages

Advantages:

- Easy to use: most commonly used design in oncology
- No need for a statistician to perform the calculations
- Does not require sample size specification: escalation is continued until excessive toxicity is seen

Disadvantages:

- Estimates of the MTD are not precise
  - **Low probability of selecting true MTD (38% is previous example)**
  - High variability of MTD estimates
- Many patients treated at sub-therapeutic doses
- Can be only used if the MTD is defined as dose with 20% toxicity probability
- Not for trials with delayed toxicity

Translation of innovative designs into Phase I trials

Rogatko et al. (JCO, 2007)

- Looked at journal articles from 1991 to 2006
- Searched TS((((phase I)OR(phase 1)OR(phase one))SAME(study or studies OR trial*)) AND cancer AND (patients OR subjects)))

- Of 1,235 articles published in 116 journals the following designs were cited

3+3 or variation	1,215 (98.4%)
CRM	17 (1.4%)
EWOC	3 (0.2%)

5+5 design

Phase 1 lymphoma study of a new radioimmunotherapy and one cycle of a proteasome inhibitor

DLT was defined as grade 4 thrombocytopenia (reduced platelet count)

Target dose is dose with DLT probability of $\Gamma = 0.1$.

PI's question: Can we use the 3+3 design and then estimate the dose with $\Gamma = 0.1$ from the data we obtain?

Use 5+5 design instead:

- If 0/5 DLTs, increase the dose
- If 1/5 DLTs, repeat the dose
  - if 1/10, increase the dose
  - if $\geq$ 2/10, STOP; if previous dose has only 5 patients, assign 5 more patients to that dose
- If 2/5 DLTs, STOP

3+3 and 5+5 designs are special cases of A+B designs (Lin and Shih, 2001; Ivanova, 2006)

3+3 design results in a very long trial if long follow-up is required for toxicity

Phase 1 trial of weekly Taxotere given concurrently with androgen ablation and adaptive external beam radiotherapy for localized high-risk adenocarcinoma of the prostate

Patients are given androgen ablation with the Luteinizing Hormone-Releasing Hormone (LHLR) agonist; 2-3 months after androgen ablation is started, the patients are given adaptive external beam radiation therapy over 8 weeks and 8 doses of weekly Taxotere chemotherapy concurrently with external radiation therapy.

That is, each patient requires at least 6 months to complete treatment.

3+3 design results in a very long trial if long follow-up is required for toxicity

Phase 1 trial of weekly Taxotere (cont)

Cohort 1, dose 10 mg/m2 1 DLT / 3
Cohort 2, dose 10 mg/m2 1? DLT / 3

1?: Patient had elevated LFTs at week 3, and according to protocol, his chemo was held until LFTs came down to an acceptable level. This grade 3 toxicity of LFT abnormalities was likely due to a medication that the patient was taking, rather than protocol treatment.

Decision: count this DLT as 0.5 DLT and assign cohort 3 to dose 1
Cohort 3, dose 10 mg/m2 0 DLT /3
Cohort 4, dose 15 mg/m2 1 DLT/ 3
Cohort 5, dose 15 mg/m2 0 DLT/ 3

Dose-finding trials with long follow-up

This was a trial of a new alkylating agent used in conjunction with other drugs for graft verses host disease (GVHD) prophylaxis in patients undergoing stem cell transplantation.

The goal was to identify the MTD defined as dose with DLT rate of 0.25.

The DLT was defined as any irreversible grade 3 or any grade 4 non-hematologic toxicity related to drug observed during the first 42 days following stem cell infusion. **Late treatment-related toxicities**, such as veno-occlusive disease of the liver, pulmonary fibrosis, or neurotoxicity were also counted as DLTs if they occurred **within 60 months** after therapy initiation.

3+3 design are not for trials with long follow-up

It is impractical to follow patients in each cohort for 60 months in the 3+3 design.

If the 3+3 design is used and patients are followed for 42 days, what is to be done if late toxicities occur?

The investigators wanted to enroll patients in the trial on a continuous basis without waiting for toxicity outcomes of the current cohort. The 3+3 design cannot handle continuous enrollment.

Other design options?

Review of dose-finding designs

	Next assignment	Model*	Data used to make decision
Escalation design	↑	No	*cohort size*
3+3 design	↑↔↓	No	3 or 6
Up-and-down design (1948)	↑↔↓	No	1
Group designs (1963)	↑↔↓	No	*cohort size, often 3-6*
Cumulative cohort design (2007)	↑↔↓	No	*all data at dose* d_i
Dose-finding based on *t*-statistic (2009)	↑↔↓	No	*all data at dose* d_i
Modified tox prob interval (mTPI) (2010)	↑↔↓	No	*all data at dose* d_i
Rapid enrollment design (RED) (2016)	↑↔↓	No	*all data at dose* d_i, d_{i+1}
Continual reassessment method (1990)	↑↔↓	Yes	*all data*
Escalation with overdose control (1998)	↑↔↓	Yes	*all data*

* ”No” means that the model is isotonic but no parametric model is assumed

Features of up-and-down designs

- For each new patient (cohort of patients) the dose is **increased, repeated or decreased**.

- The **sample size** for an up-and-down design needs to be **specified in advance**.

- Up-and-down designs assign as many subjects as possible to and around the MTD to ensure the high quality of estimation of the MTD.

- Up-and-down designs can accommodate continuous enrollment of patients and delayed toxicity outcomes.

Terminology: the term "up-and-down" is usually reserved for designs that do not use a parametric model for dose-toxicity relationship.

Up-and-down design of Dixon and Mood

Toxicology studies are studies to evaluate potential negative effects of a new compound on animals. The design frequently used is a random walk design:

Doses are chosen from the set $d_1, d_2, \ldots, d_K$

Assignments are one at a time.

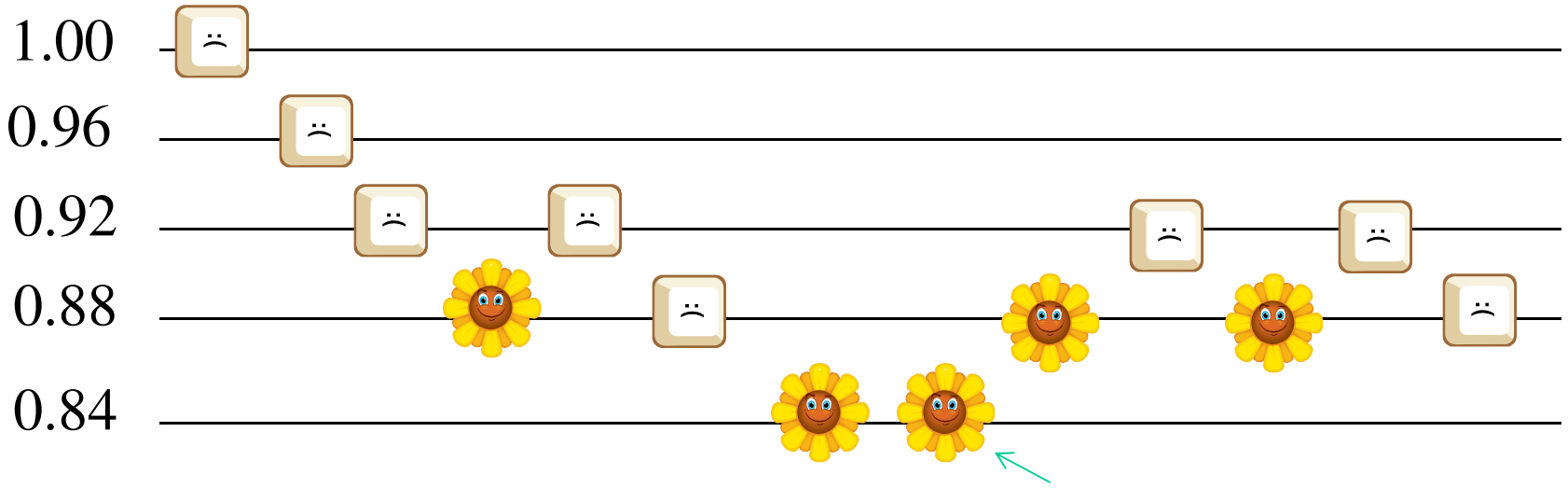
- If 0/1 toxicity is observed, assign the next subject to the next higher dose
- If 1/1 toxicity is observed, assign the next subject to the next lower dose

What dose is most frequently assigned if this design is used?

The ED_X, the dose where $X\%$ of subjects experience toxicity

Up-and-down design of Dixon and Mood

• The primary reference for Up-and-down designs (staircase designs) is Dixon and Mood (JASA, 1948). The goal is to estimate the $ED_?$



Estimated $ED_?$ is 0.88

This dose is repeated because lower doses were not considered

Up-and-down experiments

- Georg von Bekesy (1947)

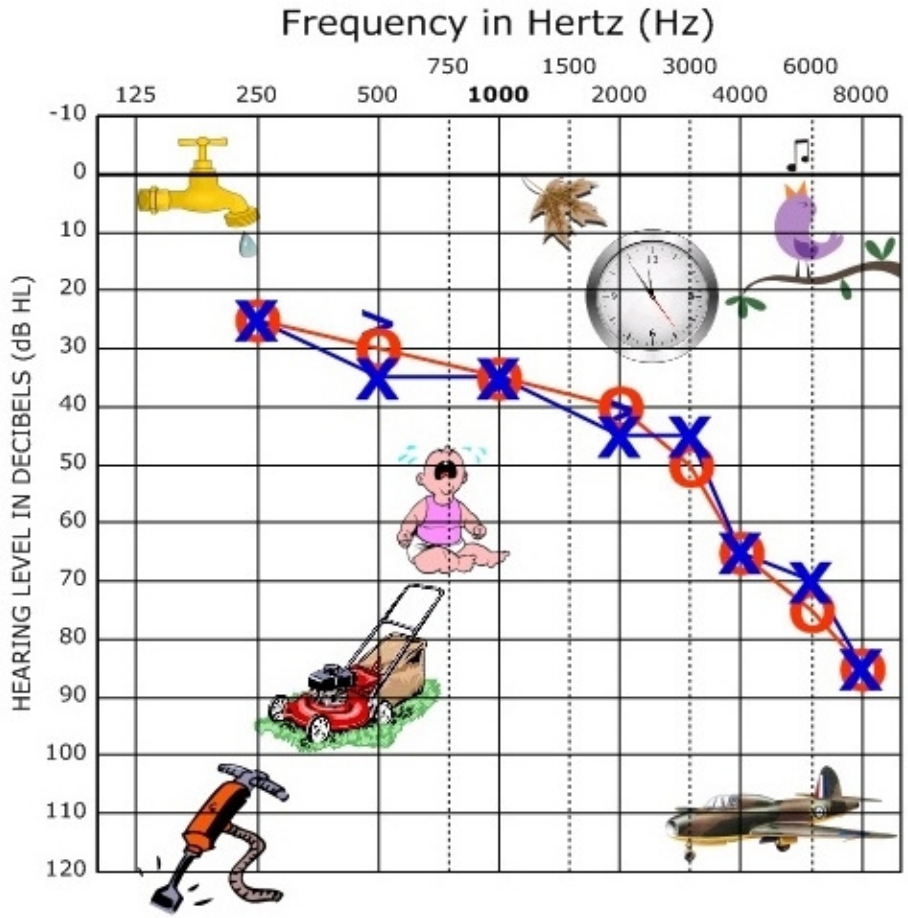
Speech Audiometry

Threshold is the level

at which a patient can

correctly repeat

50% of the words



Group random walk designs

Group random walk designs are Markov chains.

The transition probability for each transition depends on the **current dose** (state) but not on what happened before that (Markov property)

A. MAPKOB
(1856-1922)

Group up-and-down designs

Group up-and-down or random walk designs (Tsutakawa, JASA, 1967; Wetherill and Glazebrook, 1986 "*Sequential methods in statistics*")

Assign subjects in cohorts of size 3.

- If 0/3 toxicities are observed, assign the next group of 3 subjects to the next higher dose
- If 2/3 or 3/3 toxicities are observed, assign the next group of 3 subjects to the next lower dose
- If 1/3 toxicities are observed, repeat the dose for the next group of 3 subjects

Questions: If we continue this process for a sufficiently long period will we see convergence?

If yes, what dose will be the mode of the stationary distribution?

Group random walk (up-and-down) designs

If dose-response curve is strictly increasing, using Markov chain theory we can show that in large trials most assignments will be to one or two doses. The response rate at these doses, the response rate that design targets, will be close to the solution of

$$\Pr[\text{decrease dose}] = \Pr[\text{increase dose}]$$

Example 1 (Dixon and Mood, JASA, 1948)

If Γ is the probability of toxicity at current dose, then

$\Pr[\text{decrease the dose}] = \Pr(\text{toxicity}) = \Gamma$

$\Pr[\text{increase the dose}] = \Pr(\text{no toxicity}) = 1 - \Gamma$

The equation is $\Gamma = 1 - \Gamma$ and hence

$\Gamma = 0.5$

Group random walk (up-and-down) designs

Example 2

- Pr(increase the dose) = Pr[0/3] = $(1 - \Gamma)^3$

- Pr(decrease the dose) = Pr[2/3 or 3/3]
  $= 3(1 - \Gamma)\,\Gamma^2 + \Gamma^3$

$(1 - \Gamma)^3 = 3(1 - \Gamma)\,\Gamma^2 + \Gamma^3$

The solution of the equation is $\Gamma = 0.3473$

The *t*-statistic design

The *t*-statistic design can be viewed as an extension of group up-and-down designs. It can be used not only with binary outcomes but also with continuous or ordinal outcomes (Ivanova and Kim, 2009):

The most recent cohort of subjects is assigned to dose *d*. Let $\bar{Y}$ be the estimate of the mean response and S^2 be the estimate of the variance at *d*. Let *n* be the number of subjects assigned to *d* so far. Compute

$$t = \frac{\bar{Y} - 0.2}{S / \sqrt{n}}$$

(i) If $t \leq -1$, increase the dose ↑

(ii) If $-1 < t < 1$, repeat the dose ↔

(iii) If $1 \leq t$, decrease the dose ↓

Illustrating the *t*-statistic design

Level	Cohort	
1	0/3	$t = -\infty$ increase the dose
2	0/3	$t = -\infty$ increase the dose
3	0/3	$t = -\infty$ increase the dose
4	1/3 → 1/3	$t = (1/3\text{-}0.2)/\text{SE} = 0.48$ repeat the dose
		$t = (2/6\text{-}0.2)/\text{SE} = 0.66$ repeat the dose

Estimating the MTD

How to estimate the MTD in a phase 1 trial where an up-and-down design was used?

1. Take the dose with the most assignments (the mode dose) and declare it the MTD.
2. Can simply calculate $p_1 = y_1/n_1, \ldots, p_K = y_K/n_K$, where y_j is the number of toxicities at the j^{th} dose, $j = 1,\ldots,K$. Then pick the dose with estimated toxicity rate closest to Γ. Not the best method since there can be several doses with toxicity rate closest to Γ.
3. If we believe that toxicity is non-decreasing with dose, we can fit isotonic model to the data.
4. If we believe that dose-toxicity relationship follows a certain model, for example, a 2-parameter logistic, we can estimate k_0 and k_1, and then compute the MTD.

Parametric estimation

- Let $d_1,\ldots, d_k$ be an ordered set of available doses and $P(d_j)$ be a probability of toxicity at dose d_j
- Possible models for dose-toxicity relationship

  1) 2-parameter logistic model

$$P(d_j) = \frac{\exp\left(k_0 + k_1 d_j\right)}{1 + \exp\left(k_0 + k_1 d_j\right)}$$

$$\text{MTD} = \left(\ln\left[\frac{\Gamma}{1-\Gamma}\right] - \hat{k}_0 \right) / \hat{k}_1$$

  2) 4-parameter logistic

  3) Emax model

  etc

Isotonic regression estimator of the MTD

Why parametric model might not be good for the MTD estimation.
"… a parametric curve that fits the data well over the range of observed doses may be biased absurdly in the region of interest" (Schmoyer, 1986)

Isotonic model is the model where we only assume **monotonicity** of the mean response with dose (for binary or continuous outcomes).

Isotonic regression is the estimator that maximizes likelihood under isotonic restriction $p_1 \leq \ldots \leq p_K$ (Robertson, Wright, Dykstra, 1988).

Isotonic regression

Dental data (Potthoff and Roy, 1964)

Age				Sample Mean
8	21	23.5	23	22.5
10	24	21	25	23.3
12	21.5	22	19	20.8
14	23.5	25		24.25

We assume that $X_{ij} \sim N(\mu_i, \sigma^2)$, $i = 1, 2, 3, 4$, where

X_{ij} is the jth observation in group i, $i = 1, 2, 3, 4$

It is believed that mean responses in the four groups are non-decreasing with age:

$$\mu_1 \leq \mu_2 \leq \mu_3 \leq \mu_4$$

Isotonic regression

If σ^2 is known, by sufficiency we can base the likelihood on $\bar{X}_i$

We know that $\bar{X}_i \sim N\left(\mu_i, \frac{\sigma^2}{n_i}\right)$

The likelihood for group i

$$L_i(\mu_i) = \frac{1}{\sqrt{\frac{2\pi\sigma^2}{n_i}}} \exp\left\{-\frac{(\bar{X}_i - \mu_i)^2}{2\frac{\sigma^2}{n_i}}\right\} = C_i \exp\left\{-\frac{(\bar{X}_i - \mu_i)^2}{2\frac{\sigma^2}{n_i}}\right\}$$

The likelihood for all four groups

$$L = L_1 L_2 L_3 L_4 = C \exp\left\{-\frac{\sum_{i=1}^{4} (X_i - \bar{X}_i)^2 n_i}{2\sigma^2}\right\}$$

Isotonic regression

Maximizing the likelihood

$$L = \frac{1}{4\pi^2} \exp\left\{ -\frac{\sum_{i=1}^{4} (\bar{X}_i - \mu_i)^2 n_i}{2\sigma^2} \right\}$$

is equivalent to minimizing $\sum_{i=1}^{4} (\bar{X}_i - \mu_i)^2 n_i$

In the example we minimize

$(\mu_1 - 22.5)^2 3 + (\mu_2 - 23.3)^2 3 + (\mu_3 - 20.8)^2 3 + (\mu_4 - 24.25)^2 2$

over $(\mu_1, \mu_2, \mu_3, \mu_4)$ subject to $\mu_1 \le \mu_2 \le \mu_3 \le \mu_4$

Isotonic regression

Let $\bar{X}_1, \bar{X}_2, ..., \bar{X}_K$ be sample means

Denote unrestricted MLEs as $\hat{\mu}_1, ..., \hat{\mu}_K$.

Denote restricted MLEs as $\tilde{\mu}_1, ..., \tilde{\mu}_K$, $\tilde{\mu}_1 \leq ... \leq \tilde{\mu}_K$

Unrestriced MLEs are $\hat{\mu}_i = \bar{X}_i$

If sample means are ordered

$\bar{X}_1 \leq \bar{X}_2 \leq ... \leq \bar{X}_K$

then restricted MLEs are the same as unrestricted

$\tilde{\mu}_i = \hat{\mu}_i = \bar{X}_i$

If sample means are NOT ordered, how to compute restricted MLEs or alternatively how to compute restricted least squares estimator?

Isotonic regression

Theorem. Under simple order restriction (e.g., non-decreasing curve) Pool Adjacent Violators Algorithm (PAVA) computes the least squares estimator

PAVA:

Step 1. Find violation 22.5 **23.3** **20.8** 24.25

Step 2. Pool data of the violators:

(24+21+25+21.5+22+19)/6 = 22.08

Back to Step 1. Find violation **22.5** **22.08** **22.08** 24.25

Step 2. Pool data of the violators

(21+23.5+23+24+21+25+21.5+22+19)/9=22.22

Back to Step 1. Find violation **22.22** **22.22** **22.22** 24.25

Isotonic regression for binary data

Y_{ij} ~ Binomial(p_i, n_i)

Hypothetical example

Age	Observations	Observed Proportion
8	0 0 1	1/3
10	0 0 0	0/3
12	0 1 1	2/3
14	0 1	1/2

It can be shown that PAVA can be used to compute restricted MLEs for binary data as well

Step 1. Find violation	**1/3**	**0/3**	2/3	1/2
Step 2. Pool data of the violators:	**1/6**	**1/6**	2/3	1/2
Back to Step 1. Find violation	1/6	1/6	**2/3**	**1/2**
Step 2. Pool data of the violators	1/6	1/6	3/5	3/5
Back to Step 1. Find violation	1/6	1/6	3/5	3/5

Continual Reassessment Method (CRM)

- CRM is a design to find the dose with certain toxicity probability (binary outcome) on a dose-toxicity curve (O'Quigley, Pepe, Fisher, 1990)

- CRM
  - Start at the lowest level
  - Assign patients one at a time or in cohorts (2 or 3)
  - Continue until the total sample size (18-24) is reached
  - Determine the next dose for a patient based on a parsimonious model (working model)
  - Do not skip untried doses when escalating

CRM model specification

- Say we would like to use the CRM in a trial with 6 doses
- Let $\boldsymbol{d} = (d_1,\ldots, d_6)$ be the vector of 6 dose levels
- We need to specify the CRM working model, if we use "empiric" model we need to specify 6 constants $\boldsymbol{b} = (b_1,\ldots, b_6)$, e.g.

$$(b_1,\ldots, b_6) = (0.05, 0.10, 0.20, 0.30, 0.50, 0.70)$$

- The model is $P(\text{toxicity} \mid d_j,\beta) = F(d_j,\beta) = b_j^{\beta}$

- The prior for β is, for example, $f(\beta)=\exp(-\beta)$ with $\mathrm{E}(\beta) = 1$

CRM model specification

The working model can be selected by using Ken Cheung's package dfcrm

http://www.inside-r.org/packages/cran/dfcrm/docs/getprior

getprior(halfwidth, target, nu, nlevel, model = "empiric")

halfwidth	The desired halfwidth of the indifference intervals.
target	The target DLT probability.
nu	The prior guess of MTD.
nlevel	The number of test doses.
model	“empiric or “logistic”.

getprior(0.04, 0.2, 3, 6)

- If ‘nu’ is 1 or 2 CRM might be slow to escalate beyond dose 2
- If ‘halfwidth’ is large CRM might be slow to escalate
- Recommended ‘halfwidth’ value is 0.25Γ .

CRM, how to compute the next dose?

- Assign the first patient to dose $x_1 = d_1$ and observe response y_1 ($y_1 = 0$ if no toxicity, $y_1 = 1$ if toxicity). Update the distribution of parameter a using the data (x_1, y_1) and Bayes theorem

$$f_{B|Y}(\beta \mid y_1) = \frac{\Pr\{Y = y_1 \mid \beta\} f(\beta)}{\Pr\{Y = y_1\}}$$

$$= \frac{F(x_1, \beta)^{y_1} \left[1 - F(x_1, \beta)\right]^{1-y_1} f(\beta)}{\int F(x_1, u)^{y_1} \left[1 - F(x_1, u)\right]^{1-y_1} f(u)\, du}$$

CRM, how to compute the next dose?

- Calculate posterior mean of β

$$\beta^{(2)} = \int \beta \, f_{A|Y}(\beta \mid y_1) \, d\beta$$

$$= \frac{\int \beta \, F(x_1, \beta)^{y_1} \left[1 - F(x_1, \beta)\right]^{1-y_1} f(\beta) \, d\beta}{\int F(x_1, u)^{y_1} \left[1 - F(x_1, u)\right]^{1-y_1} f(u) \, du}$$

To implement the Bayesian CRM we need to compute two integrals. One can use numerical integration and approximate the integrals with summation.

- Dose x_2 for patient 2 is chosen in such a way that

$$F(x_2, \beta^{(2)}) = \Gamma$$

or $F(x_2, \beta^{(2)})$ is the closest to Γ if a discrete set of doses is considered.

Repeat until the total sample size is reached.

CRM, how to compute the next dose?

- Calculating posterior mean of β after one patient is assigned to d_1

$$\beta^{(2)} = \frac{\int_{a=0}^{\infty} \beta \left(b_1^{\beta}\right)^{y_1} \left(1 - b_1^{\beta}\right)^{1-y_1} f(\beta)\, d\beta}{\int_{u=0}^{\infty} \left(b_1^{u}\right)^{y_1} \left(1 - b_1^{u}\right)^{1-y_1} f(u)\, du}$$

- Calculating posterior mean of β after 3 patients are assigned to d_1

$$\beta^{(2)} = \frac{\int_{a=0}^{\infty} \beta \left(b_1^{\beta}\right)^{y_1+y_2+y_3} \left(1-b_1^{\beta}\right)^{3-(y_1+y_2+y_3)} f(\beta)\, d\beta}{\int_{u=0}^{\infty} \left(b_1^{u}\right)^{y_1+y_2+y_3} \left(1-b_1^{u}\right)^{3-(y_1+y_2+y_3)} f(u)\, du}$$

CRM, how to compute the next dose?

- Calculating posterior mean of a after 3 patients are assigned to d_1 and no DLTs are observed, that is, $y_1 = y_2 = y_3 = 0$

$$\beta^{(2)} = \frac{\int_{\beta=0}^{\infty} \beta \left(b_1^{\beta}\right)^{y_1+y_2+y_3} \left(1-b_1^{\beta}\right)^{3-(y_1+y_2+y_3)} f(\beta)\, d\beta}{\int_{u=0}^{\infty} \left(b_1^{u}\right)^{y_1+y_2+y_3} \left(1-b_1^{u}\right)^{3-(y_1+y_2+y_3)} f(u)\, du}$$

$$= \frac{\int_{\beta=0}^{\infty} \beta \left(1-b_1^{\beta}\right)^{3} f(\beta)\, d\beta}{\int_{u=0}^{\infty} \left(1-b_1^{u}\right)^{3} f(u)\, du} = 1.49$$

CRM, how to compute the next dose?

- Dose x_2 for the next patient is chosen in such a way that

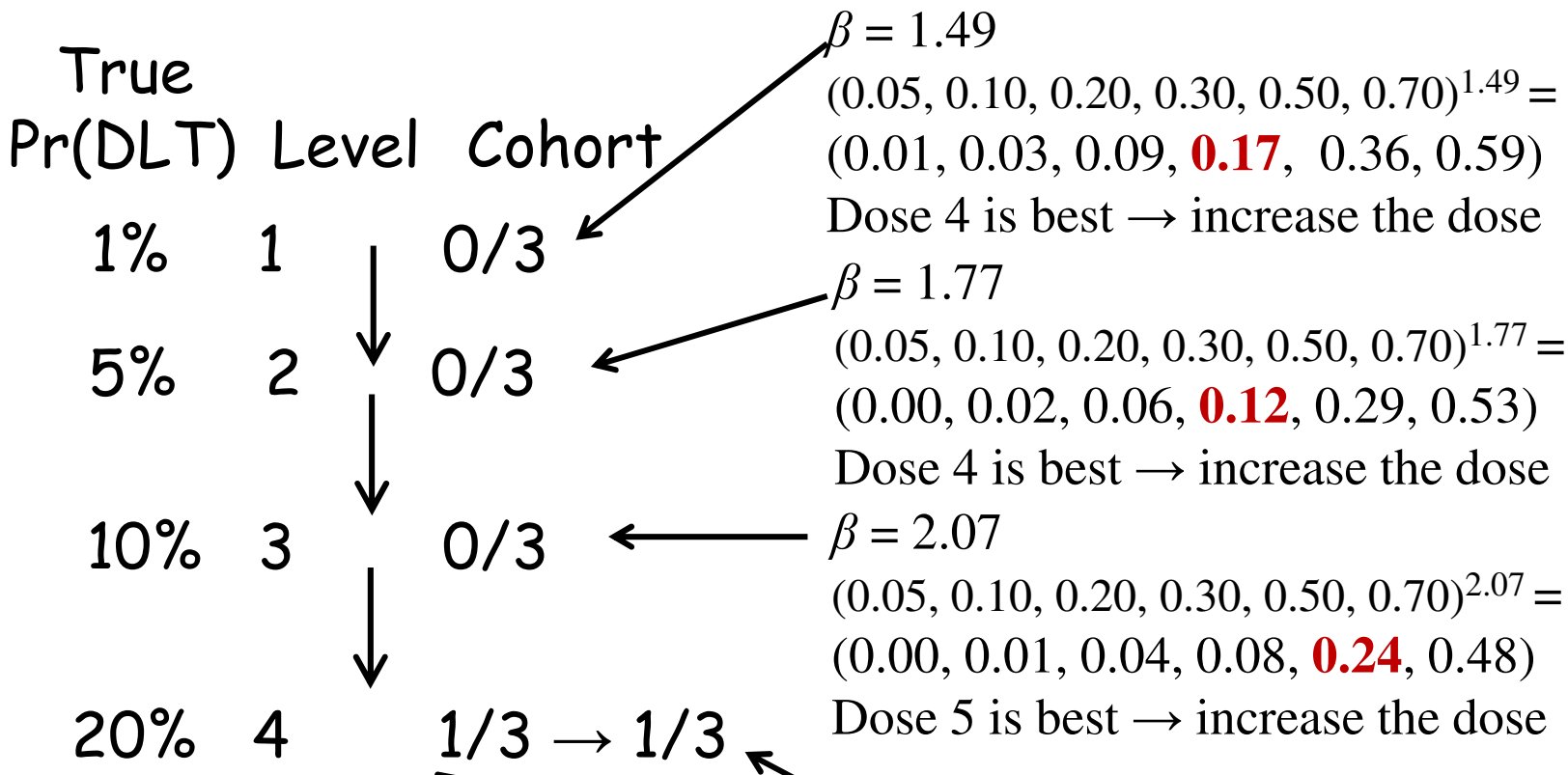
$$F(x_2, \beta^{(2)}) = \Gamma$$

or $F(x_2, \beta^{(2)})$ is the closest to Γ if a discrete set of doses is considered.

$$(0.05, 0.10, 0.20, 0.30, 0.50, 0.70)^{\beta(2)} =$$
$$(0.05, 0.10, 0.20, 0.30, 0.50, 0.70)^{1.49} =$$
$$(0.05^{1.49}, 0.10^{1.49}, 0.20^{1.49}, 0.30^{1.49}, 0.50^{1.49}, 0.70^{1.49}) =$$
$$(0.01, 0.03, 0.09, \mathbf{0.17}, 0.36, 0.59)$$

The next dose is d_4. Since we do not skip untried doses for safety reasons, the next dose is the next higher dose, d_2.

Illustrating the difference between 3+3 and CRM



More about CRM model

- CRM uses working model for the dose-toxicity relationship, one-parameter model is recommended. For example, the working model can be a one-parameter model with parameter β

$$P\left(d_j, \beta\right) = \left[\left(\tanh d_j + 1\right)/2\right]^{\beta} = \left(b_j\right)^{\beta}, \text{ where } \tanh(d) = \frac{e^{2d} - 1}{e^{2d} + 1}$$

- Many other one-parameter models, such as one-parameter logistic with fixed slope b_0 are equivalent to the above model.

$$P\left(d_j, \beta\right) = \frac{\exp(\beta + b_0 d_j)}{1 + \exp(\beta + b_0 d_j)}$$

Note that the empiric model is not equivalent to the one-parameter logistic with fixed intercept

- CRM convergence has been proven for the one-parameter tanh working model (Shen and O'Quigley, 1996). There are no results on CRM convergence when working model is a two-parameter model.

Working model

Let "doses" be $\boldsymbol{d}$ = (-1.47, -1.1, -.69, -.42, 0 , .42),

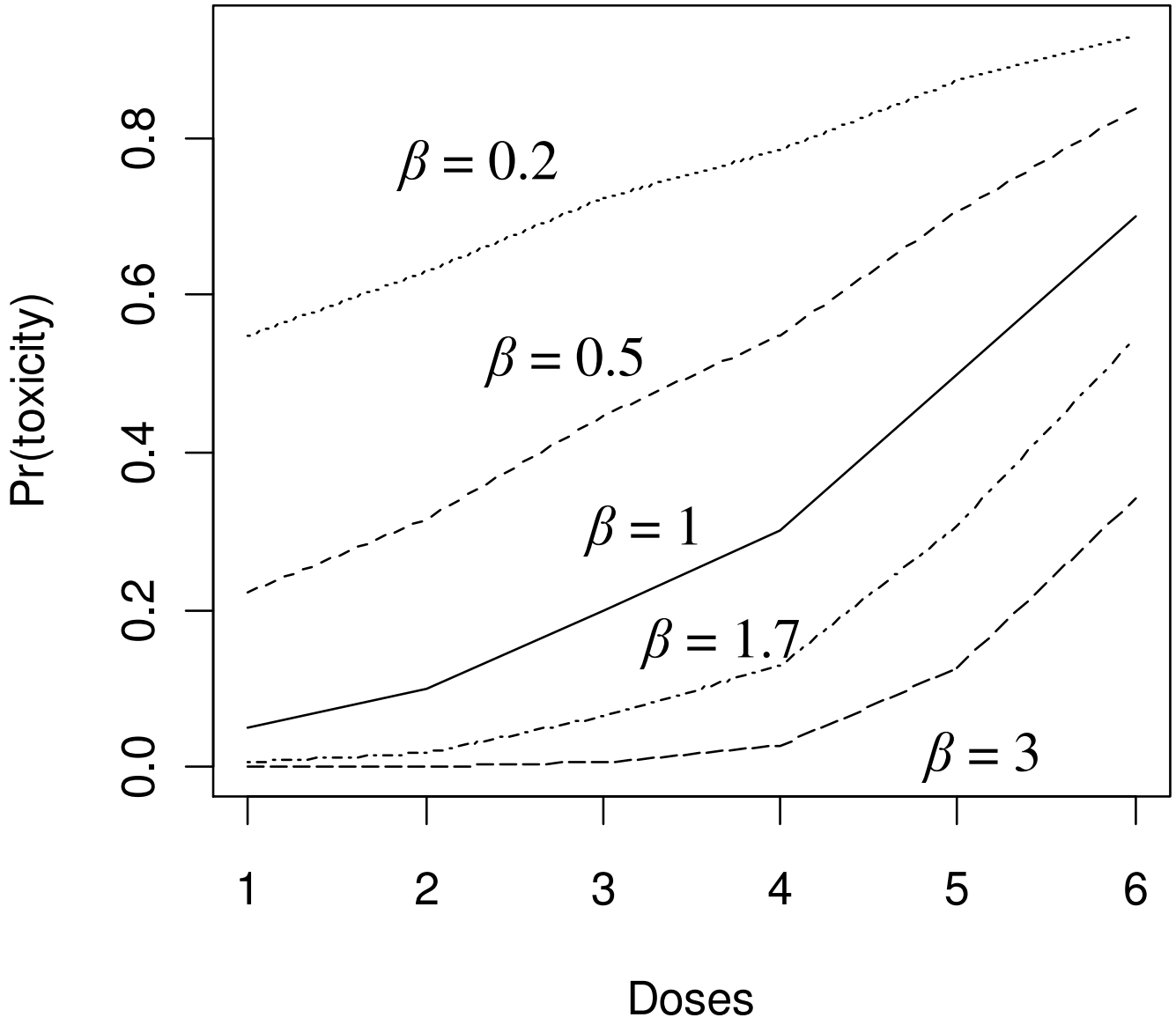
$b_j = (\tanh d_j + 1)/2$

$\boldsymbol{b} = (b_1,\ldots, b_6) = (0.05, 0.10, 0.20, 0.30, 0.50, 0.70)$

Below are toxicity rates for the working model $P(\text{toxicity}|d_j,\beta) = b_j^{\beta}$ for different values of parameter β.

$\boldsymbol{b}^{\beta}$	d_1	d_2	d_3	d_4	d_5	d_6
$\boldsymbol{b}^{1.7}$	0.01	0.02	0.07	0.13	0.31	0.54
$\boldsymbol{b}^{1}$	0.05	0.10	0.20	0.30	0.50	0.70
$\boldsymbol{b}^{0.5}$	0.22	0.32	0.45	0.54	0.69	0.80

$P(\text{toxicity}|d_j,\beta) = b_j^{\beta}$ for various values of β

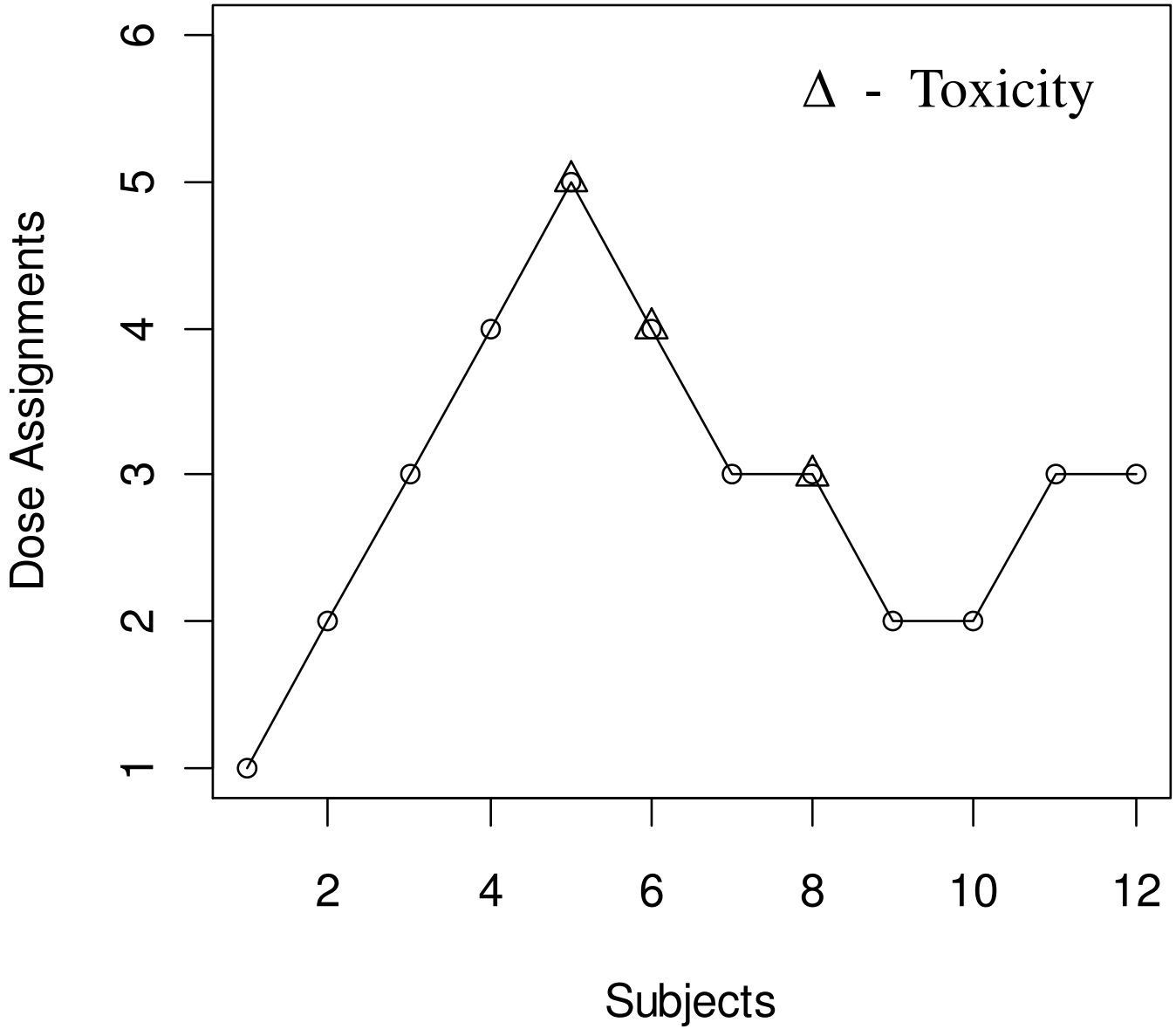


Example of a CRM trial

Target $\Gamma = 0.2$, total sample size is 12, starting dose is d_1
True toxicity rates at 6 doses are (0.11, 0.14, **0.20**, 0.25, 0.31, 0.38)
$Y = 1$, if toxicity, and 0 if no toxicity

Subject number	Dose	Total subjects	y	Toxicity vector	$\beta^{(n)}$	$P(\text{tox}\|\beta^{(n)}) = \boldsymbol{b}^{\beta^{(n)}}$	Next dose
1	d_1	**1**,0,0,0,0,0	0	**0**,0,0,0,0,0	1.27	0.02,0.05,0.13,**0.22**,0.41,0.64	d_2
2	d_2	1,**1**,0,0,0,0	0	0,**0**,0,0,0,0	1.44	0.01,0.04,0.10,**0.18**,0.37,0.60	d_3
3	d_3	1,1,**1**,0,0,0	0	0,0,**0**,0,0,0	1.63	0.01,0.02,0.07,**0.14**,0.32,0.56	d_4
4	d_4	1,1,1,**1**,0,0	0	0,0,0,**0**,0,0	1.84	0.00,0.01,0.05,0.11,**0.28**,0.52	d_5
5	d_5	1,1,1,1,**1**,0	1	0,0,0,0,**1**,0	1.30	0.02,0.05,0.12,**0.21**,0.41,0.63	d_4
6	d_4	1,1,1,**2**,1,0	1	0,0,0,**1**,1,0	0.91	0.06,0.12,**0.23**,0.33,0.53,0.72	d_3
7	d_3	1,1,**2**,2,1,0	0	0,0,**0**,1,1,0	1.00	0.05,0.10,**0.20**,0.30,0.50,0.70	d_3
8	d_3	1,1,**3**,2,1,0	1	0,0,**1**,1,1,0	0.76	0.10,**0.18**,0.30,0.40,0.59,0.76	d_2
9	d_2	1,**2**,3,2,1,0	0	0,**0**,1,1,1,0	0.81	0.09,**0.16**,0.27,0.38,0.57,0.75	d_2
10	d_2	1,**3**,3,2,1,0	0	0,**0**,1,1,1,0	0.86	0.08,0.14,**0.25**,0.36,0.55,0.74	d_3
11	d_3	1,3,**4**,2,1,0	0	0,0,**1**,1,1,0	0.92	0.06,0.12,**0.23**,0.33,0.53,0.72	d_3
12	d_3	1,3,**5**,2,1,0	0	0,0,**1**,1,1,0	0.97	0.05,0.11,**0.21**,0.31,0.51,0.71	d_3

Example of a CRM trial



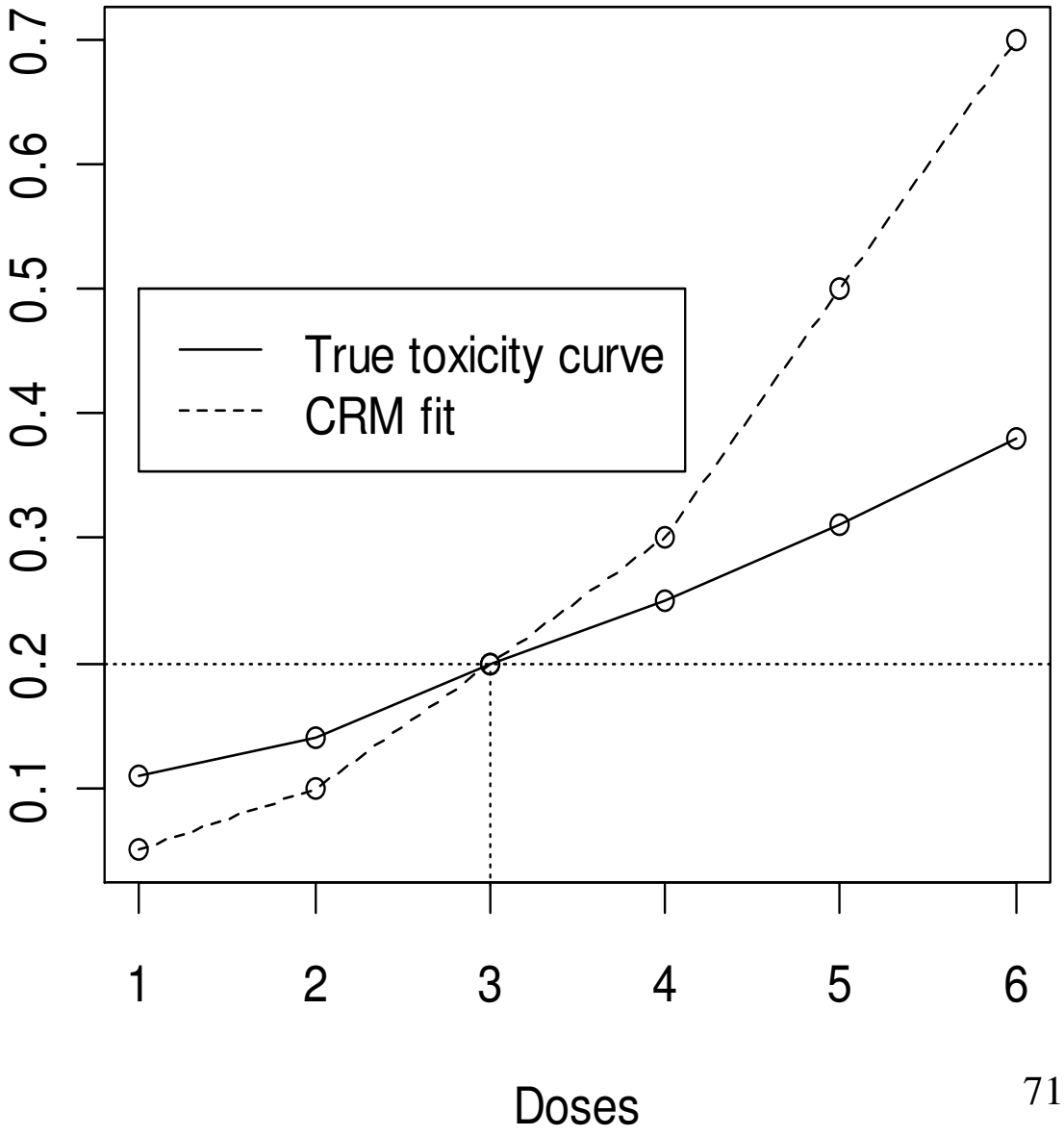
Comments about CRM

Comment 1.

CRM does NOT provide a good approximation of the WHOLE DOSE-TOXICITY CURVE.

There is no intention to approximate **the whole** dose-toxicity curve with the CRM.

All the CRM is doing (and this is all we need) is providing a good approximation at the target dose itself!



Comments about CRM

Comment 2.
The CRM ONE-PARAMETER model SHOULG NOT BE FIT THROUGH 2 POINTS AT THE SAME TIME, e.g. in a dose-finding study where some subjects in each cohort are assigned to placebo, for example.

Consider a trial as in the previous example but every time a subject is assigned according to the CRM, another subject is assigned to dose 1. All data available are used to update the mean of β in the CRM to compute the new dose.

Because the CRM provides good approximation at one dose only, fitting a CRM curve through 2 points will lead to bias in the estimation of dose-toxicity rate at both points.

Comments about CRM

Comment 3.
When Bayesian version of the CRM is used, one can NOT incorporate existing information about dose-toxicity curve though prior on β and/or the choice of skeleton.

In most cases, it is impossible to incorporate existing information about dose-toxicity curve. The exception is when we start experimentation at our best guess for the location of the target dose.

The prior on a and the skeleton are chosen to provide good operational characteristics for the CRM.

Behavior of the CRM
as the number of subjects goes to infinity

• When the CRM is used in **continuous dose space** the CRM converges to the target dose (Shen and O'Quigley, 1996).

Continuous dosing is rarely used in dose-finding trials.

Behavior of the CRM as the number of subjects goes to infinity

- When the CRM is used with adiscrete dose space, there are some sets

  $$\Gamma \ + \text{skeleton} \ + \ \text{true toxicity curve}$$

  for which the CRM might **not converge to the true target but will converge to dose(s) nearby** (Shen and O'Quigley, 1996; Cheung and Chappell, 2002; O'Quigley, 2006). Nearby doses will have toxicity probability relatively close to the target.

  For example, if the true toxicity probabilities are

  $$(0.00, 0.00, 0.03, 0.05, 0.11, \mathbf{0.22})$$

  the CRM with the working model $P(d_j,\beta) = b_j^{\beta}$ with

  $$(b_1,\ldots, b_6) = (0.05, 0.10, 0.20, 0.30, 0.50, 0.70)$$

  might converge to dose 5, not dose 6 (example from Cheung and Chappell, 2002)

Illustration on non-convergence of the CRM

Toxicity scenarios

I	0.05	0.10	0.20	0.30	0.50	0.70
II	**0.00**	**0.00**	**0.03**	**0.05**	**0.11**	**0.22**

Reported is the proportion of trials each dose was selected as the target (% recommendation) and average number of subjects allocated to each dose

	% recommendation						*Allocation*					
Scenario I												
n = 25	0.01	0.20	**0.49**	0.29	0.02	0.00	4.0	6.4	**8.6**	5.2	0.7	0.0
n = 48	0.00	0.14	**0.63**	0.23	0.00	0.00	4.2	10.3	**21.3**	11.4	0.8	0.0
Scenario II												
n = 25	0.00	0.00	0.00	0.10	0.61	**0.29**	3.0	3.0	3.2	4.9	7.5	**3.4**
n = 48	0.00	0.00	0.00	0.02	0.60	**0.38**	3.0	3.0	3.2	6.1	21.6	**11.1**

Advantages of the CRM

- For estimation of the location of the target dose,
  the CRM has been shown to work well even in trials with relatively **small total sample size.**

  Though it might not converge to the true target dose for some target probability – skeleton – dose-toxicity triplets, when it converges it performs very well.

  When it does not converge to the correct MTD it will converge to a dose with toxicity probability close to the target.

Disadvantages of the CRM

- The CRM cannot be used to estimate an entire dose-toxicity curve, it estimates the target dose only.

- It is hard to extend the CRM to
  - trials with ordinal toxicity outcome,
  - trials with continuous outcome.

  In such trials, one can use the design based on the *t*-statistic (Ivanova and Kim, 2009; Ivanova and Murphy, 2009).

Delayed outcome

- Often it takes a long time to observe toxicity. DLT is defined as toxicity in a time interval $(0,T)$, where T can be 6 weeks or 6 months as in the earlier example.

- What to do if we need to enroll a patient while some patients are still in follow-up?

- A number of methods have been developed for dose-finding with delayed outcome. For example:
  - Time to Event CRM (TITE-CRM) by Cheung and Chappell (2000), a patient with a partial follow-up contributes approximately as **a fraction of a patient WITHOUT a DLT**
  - RED (2016), conservative approach where a patient with a partial follow-up contributes as **a patient with a fraction of a DLT**

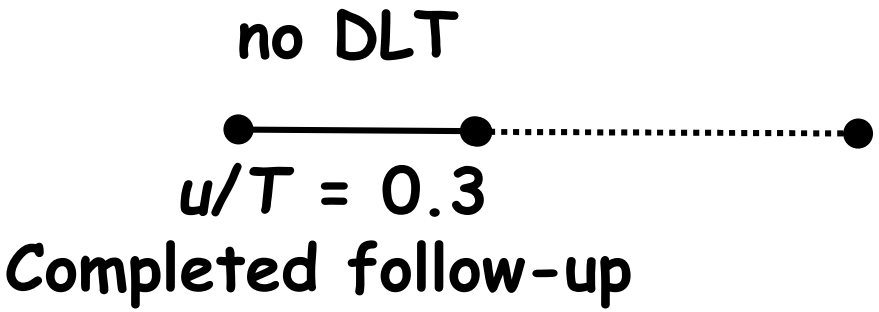
Mitigating uncertainty from patients still in follow-up

- T is the length of follow-up for DLT
- u is the follow-up time of a patient
- 1-u/T is the proportion of follow-up time still remaining
- **RED: the patient is counted as a patient with 1-u/T of a DLT**

Example. $u/T = 0.3$

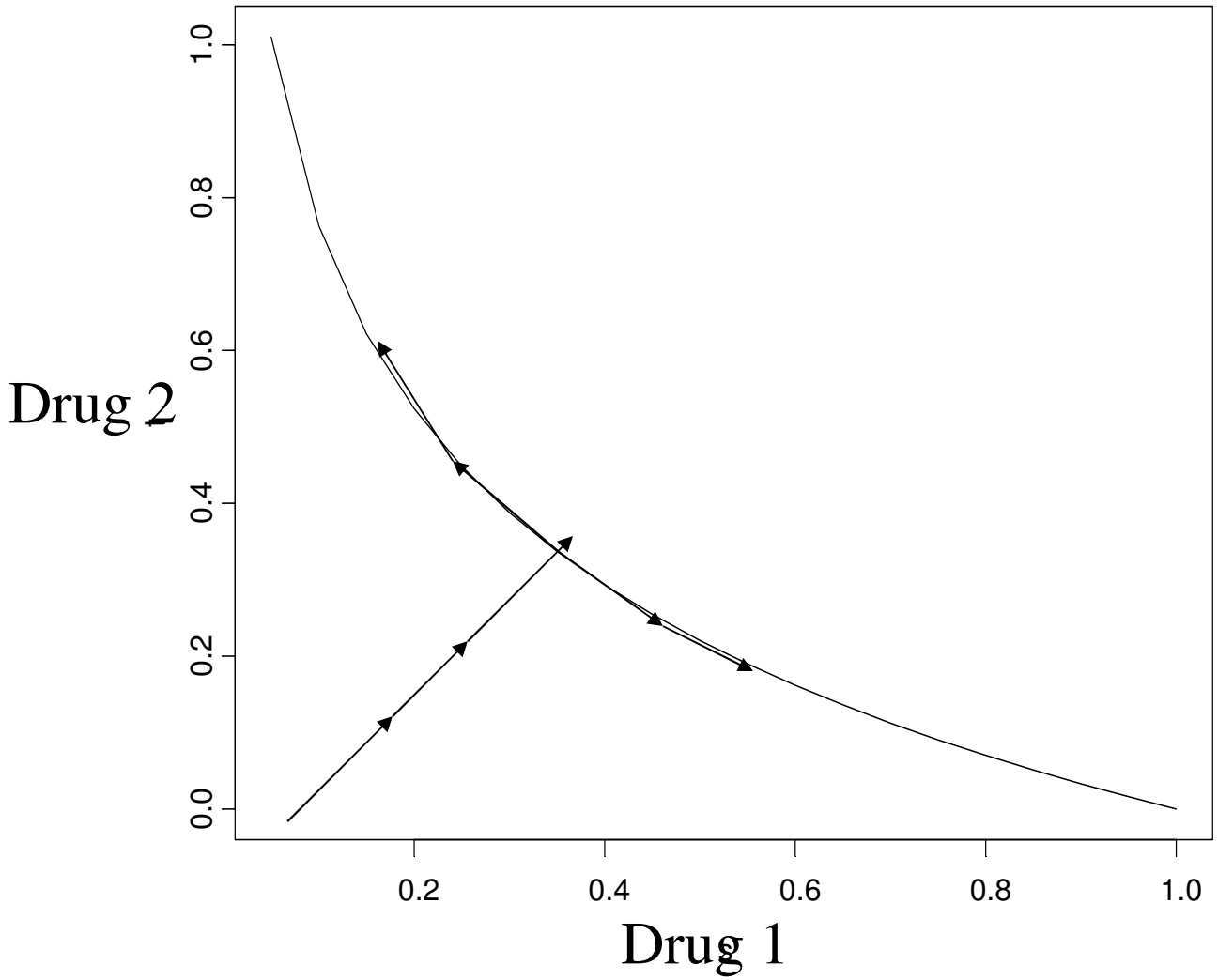
Patient's contribution **≈ 0/0.3** (TITE-CRM)

0.7/1 (RED)



Phase 1 trials with two agents

Design of Thall, Millikan, Mueller, and Lee (2003)



Phase 1 trials with two agents

Design of Kramar, Lebecq, and Candalh (1999)

(4,1)	(4,2)	(4,3)	**(4,4)**
(3,1)	(3,2)	(3,3)	**(3,4)**
(2,1)	**(2,2)**	**(2,3)**	**(2,4)**
(1,1)	**(1,2)**	(1,3)	(1,4)

Phase 1 trials with ordered groups

UGT1A1 genotype might help predict the occurrence of severe neutropenia during irinotecan therapy (Innocenti et al, 2004).

Patients with the TA indel 7/7 genotype had much higher risk of developing grade 4 neutropenia than other patients.

The probability of DLT for the population with genotype 7/7 is the same or greater than the probability of DLT at the same dose for the second population (populations are *ordered*).

One can expect that the MTD (mg/m^2) for irinotecan is lower for patients with 7/7 genotype compared to other patients.

Phase 1 trials with ordered groups

	dose 1	dose 2	dose 3	dose 4
7/7 genotype	0.05	0.10	**0.20**	0.40
others	0.05	0.08	0.13	**0.23**

Only about 10% of patients have the TA indel 7/7 genotype. Hence conducting a separate trial in TA indel 7/7 genotype subpopulation is not feasible. The only solution is to use the information from other subpopulation or to conduct a joint trial.

Isotonic design: Ivanova and Wang (2006)

CRM extension: Wages et al. (2014), an R package **POCRM**

Example: NGX267 trial

New compound for treating memory and cognitive disturbances, might offer benefit to Alzheimer's patients

NEUROGENETICS
TorreyPines

Phase 1, single dose trial
in healthy volunteers

Two outcomes of interest:
severe adverse events
moderate adverse events

The target dose is the maximum dose that is tolerable.

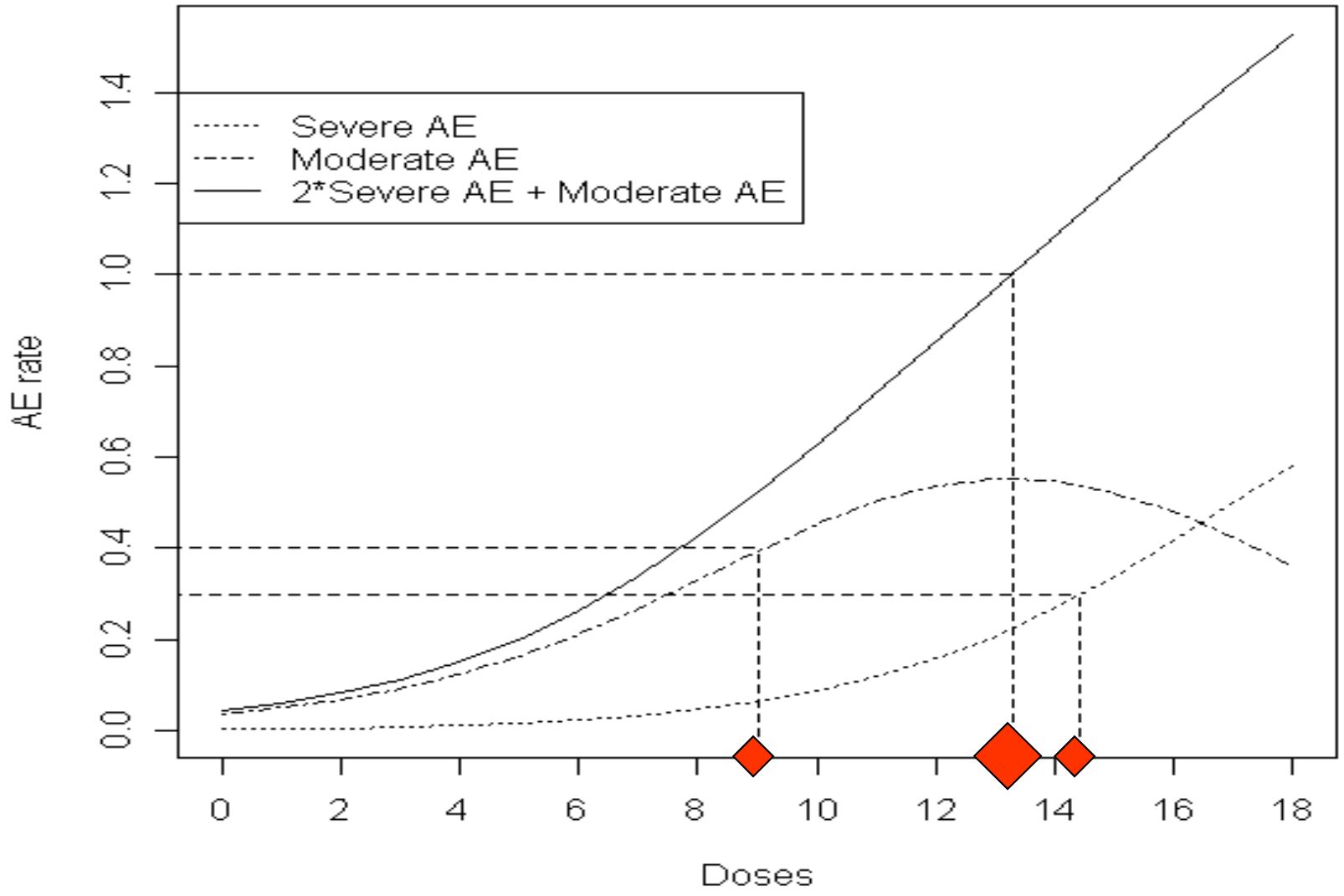
How to define the target dose?

The MTD can be defined as the highest dose such that

$$\Pr[\text{severe AE}] \leq 0.3,$$
$$\Pr[\text{moderate AE}] \leq 0.4,$$

Similar approach was taken in Paul, Rosenberger, Flournoy (2004)

How to define the target dose?



The target dose in NGX267 trial

To reflect the trade-off between severe and moderate adverse events rates, decided to define the target dose as

2*Pr[severe AE]+ Pr[moderate AE] = 1

For example,

$$2*0.3 + 0.4 = 1$$

In oncology, the target dose is sometimes defined as the dose with a certain weighted sum of probabilities of toxicity grades (Bekele and Thall, 2004; Ivanova, 2006).

Possible design for NGX267 study

• First in man studies normally involve extensive PK sampling at ALL doses, therefore at least 6 subjects are assigned at each dose. Subjects are assigned starting with the lowest dose until unacceptable rate of AEs is observed

Dose	1 mg	2.5 mg	5 mg	10 mg	15 mg	25 mg	35 mg	45 mg
Pts	6	6	6	6	6	6	6	6

• Investigators in NGX267 study believed that it is essential to get PK data at the MTD but not essential to get PK data at other doses

Design for NGX267 study

- A start-up rule, 2 drug + 1 placebo

- The start-up is followed by the cumulative cohort design,

  4 drug + 2 placebo

- No stopping rule: the total sample size was specified in advance.

Start-up rule

The goal of the start-up rule was to bring the trial to doses close to target.

Start-up was used with doses 5, 10, 15, 25, 35, 45, 60, 80, and 100 mg with 2 patients per cohort + 1 placebo.

The start-up was to be terminated as soon as the observed

$$2*\Pr[\text{severe AE}] + \Pr[\text{moderate AE}]$$

computed for subjects who received current dose of the drug is higher than 1 (escalation design).

Study design for NGX267 trial

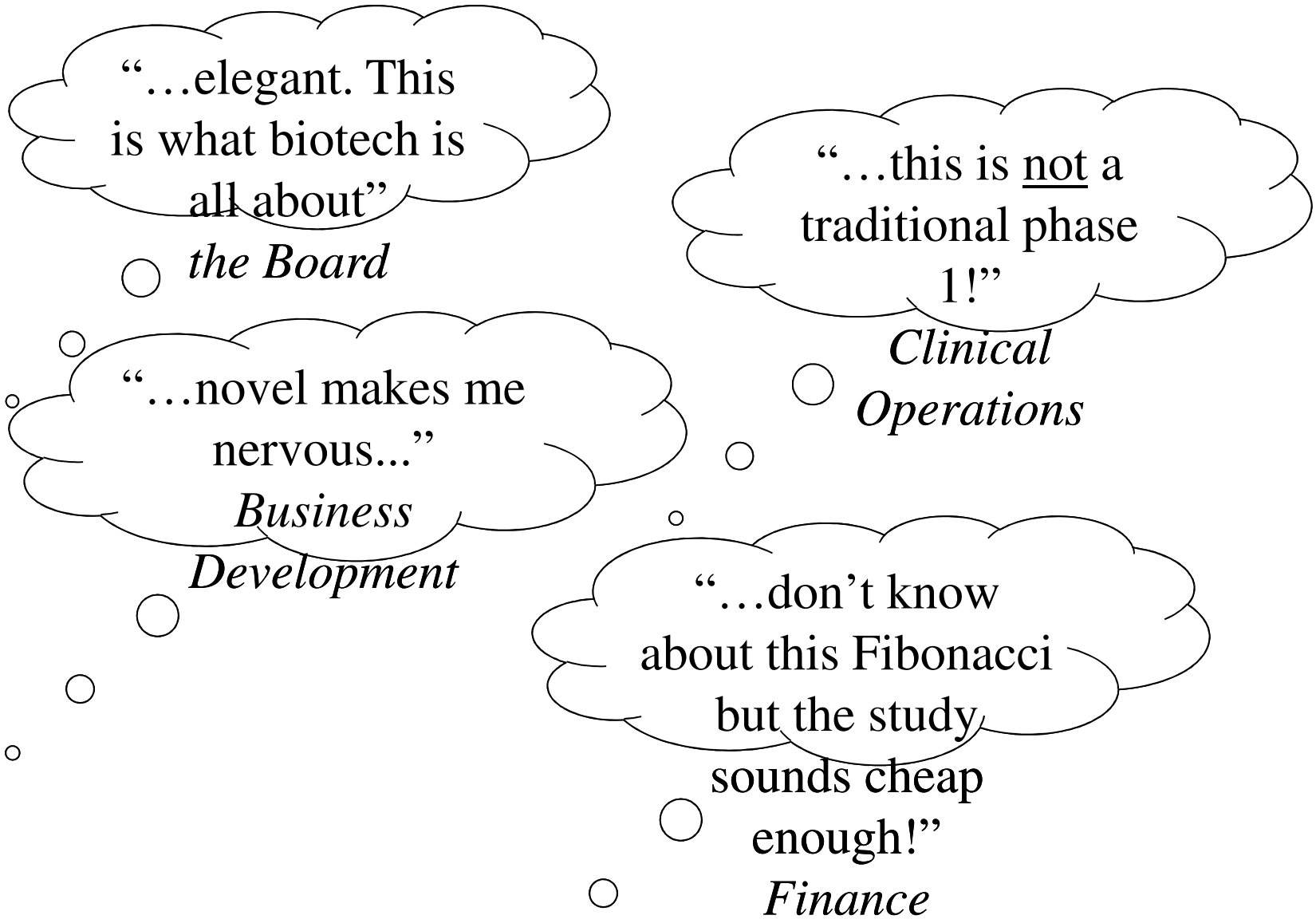
- **Cumulative cohort design** with the target of 1 +- 0.2.
  Let p = observed rate 2*(severe AE) + (moderate AE)
  - If $p \leq 0.8$, *increase* the dose;
  - If $0.8 < p < 1.2$, *repeat* the dose;
  - If $p \geq 1.2$, *decrease* the dose.

- Additional doses 20, 30, 40, 50, 70, 90 mg.

- Subjects were assigned in cohorts of 4 + 2 on placebo.

- The total sample size was set to 40 – 42 on treatment.

NGX267 Trial



Modifications suggested by FDA

FDA suggestions

1. *Add 2 more doses in the lower range*.

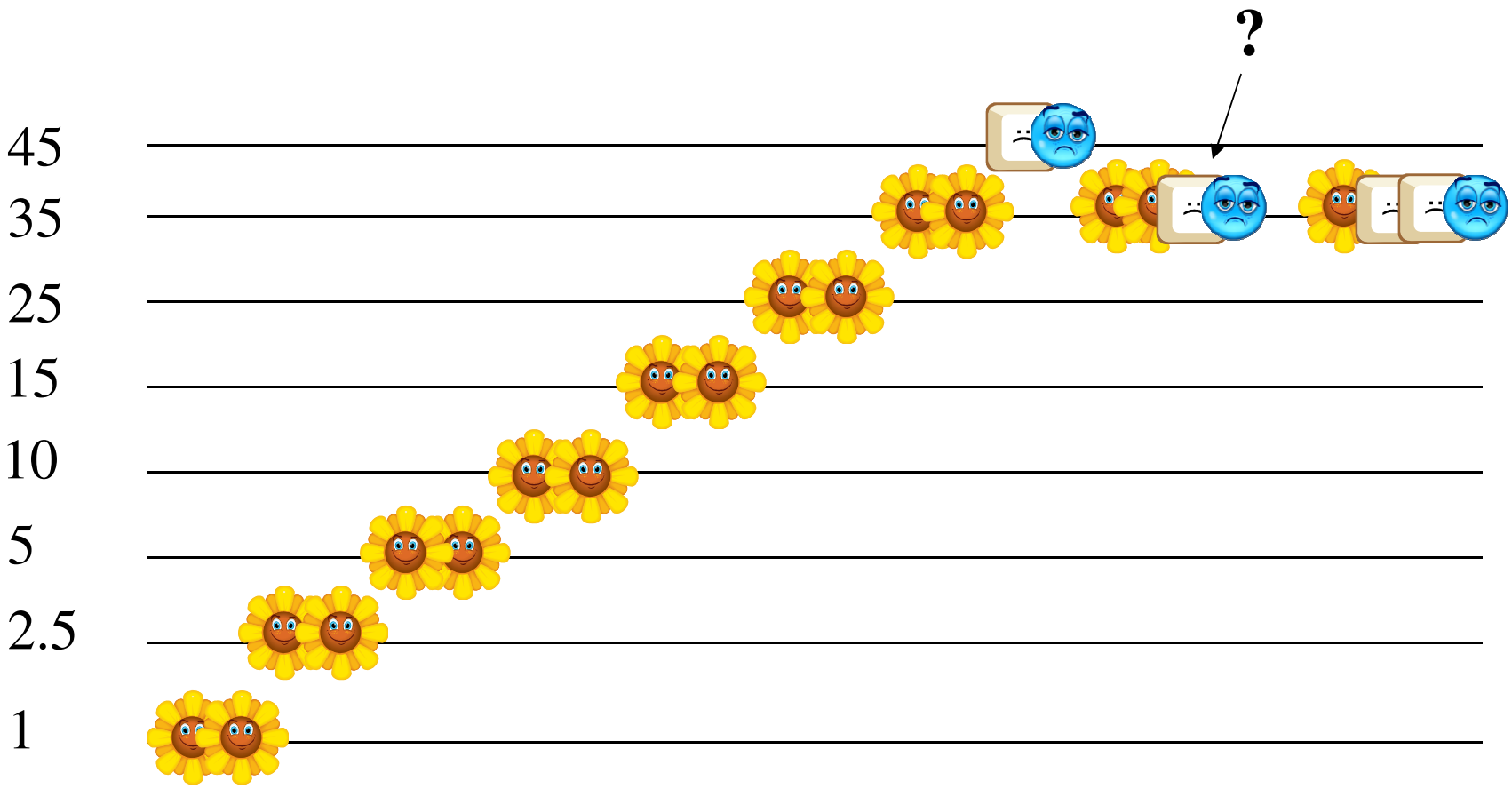
Doses 1 and 2.5 mg have been added.

2. *Change the definition of the target dose to a more conservative one*.

The definition was changed to

2*Pr[severe AE] + Pr[moderate AE] = **0.75**

NGX267 Trial: Dose Allocation



Estimated target dose is 35 mg

NGX267 trial: dose allocation

↑ Increase dose
↓ Decrease dose
↔ Repeat dose

Cohort	Dose (mg)	Total subjects	AEs last group	AEs total at current dose	*p*	Decision
1	1	2	(2, 0, 0)(2)	(2, 0, 0)(2)	0.00	↑
2	2.5	2	(2, 0, 0)(2)	(2, 0, 0)(2)	0.00	↑
3	5	2	(2, 0, 0)(2)	(2, 0, 0)(2)	0.00	↑
4	10	2	(2, 0, 0)(2)	(2, 0, 0)(2)	0.00	↑
5	15	2	(2, 0, 0)(2)	(2, 0, 0)(2)	0.00	↑
6	25	2	(2, 0, 0)(2)	(2, 0, 0)(2)	0.00	↑
7	35	2	(2, 0, 0)(2)	(2, 0, 0)(2)	0.00	↑
8	45	2	(0, 1, 1)(2)	(0, 1, 1)(2)	1.50	↓
9	35	4	(2, 1*, 1)(4)	(4, 1, 1)(6)	0.58	↔
10	35	4	(1, 2, 1)(4)	(5, 3, 2)(10)	0.75	Terminate

*This AE was somewhat in between moderate and severe and there was scored 1.5 and not 1 as a moderate AE would have been scored

NGX267 trial

Adaptive design resulted in the following allocation:

Dose	1 mg	2.5 mg	5 mg	10 mg	15 mg	25 mg	35 mg	45 mg
Pts	2	2	2	2	2	2	10	2

24 drug + 10 placebo

Compare to the design that assigns 6 subjects per dose:

Dose	1 mg	2.5 mg	5 mg	10 mg	15 mg	25 mg	35 mg	45 mg
Pts	6	6	6	6	6	6	6	6

48 drug + 16 placebo

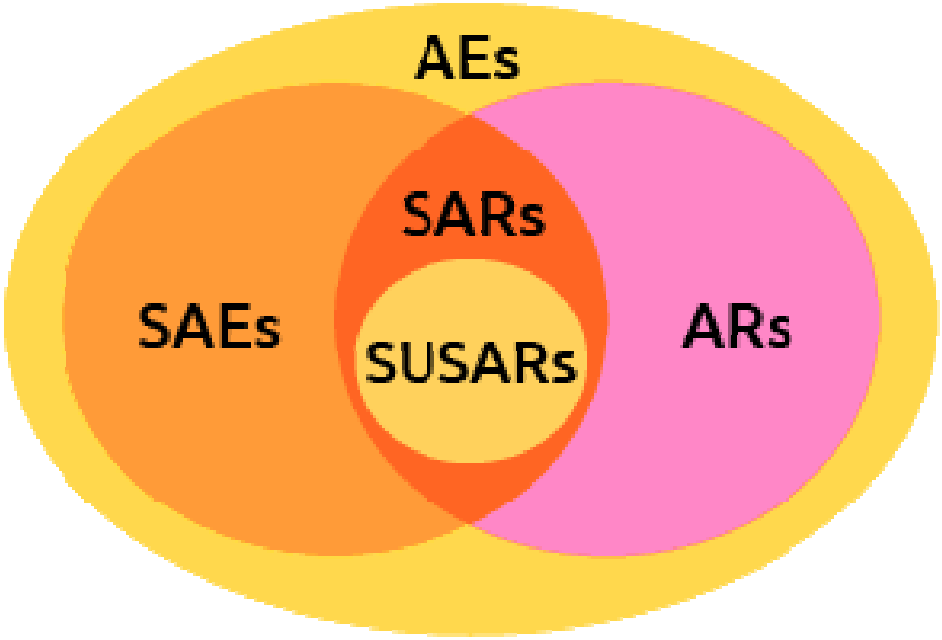
NEUROGENETICS

↓

TorreyPines

Torrey Pines Golf Course

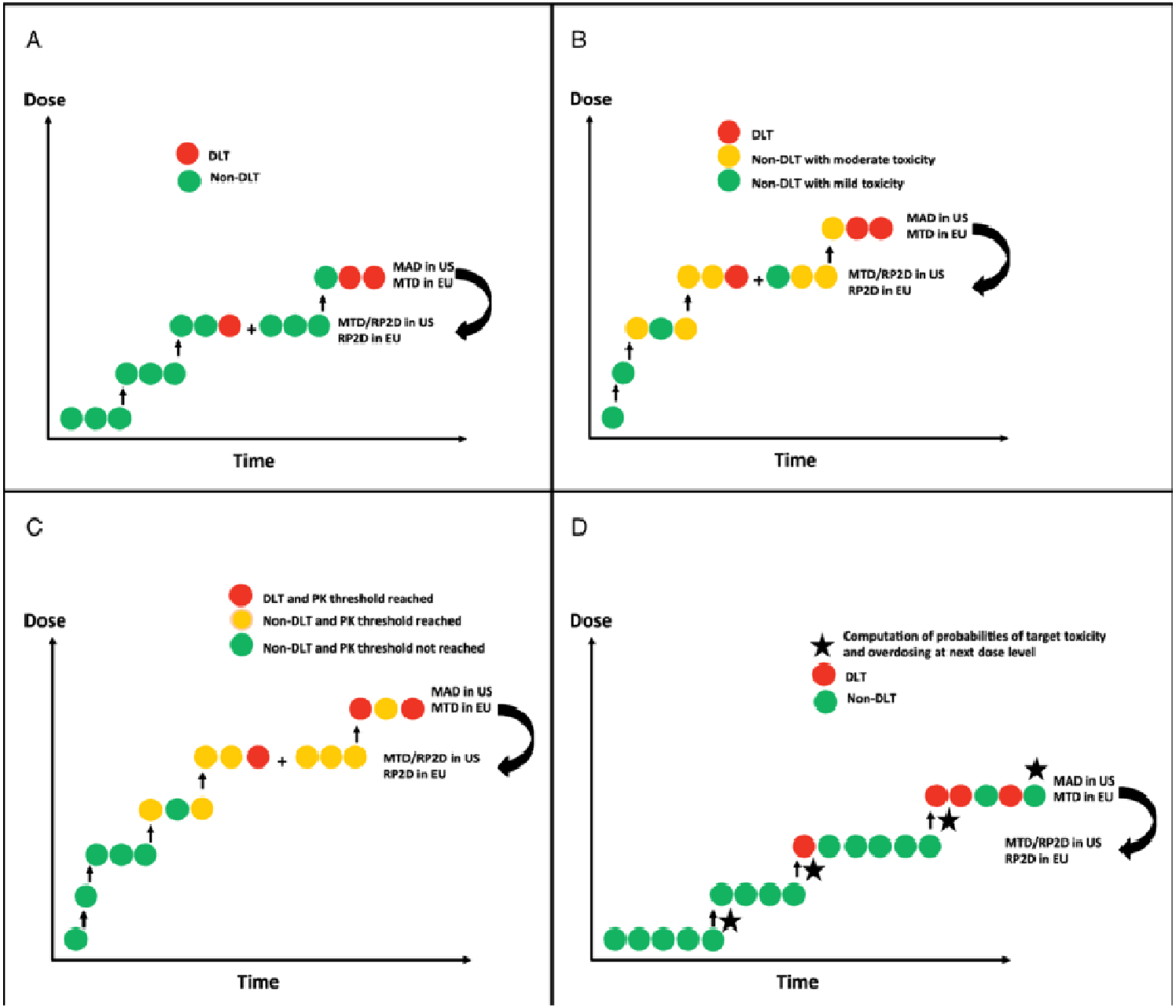
"Two things I do not like about your company — the 'neuro' and the 'genetics' in the name"


AEs
SARs
SAEs
SUSARs
ARs


None
0
1-2-3
4-5-6-7
8-9-10


PAREXEL


The French
Phase I Trial
Disaster

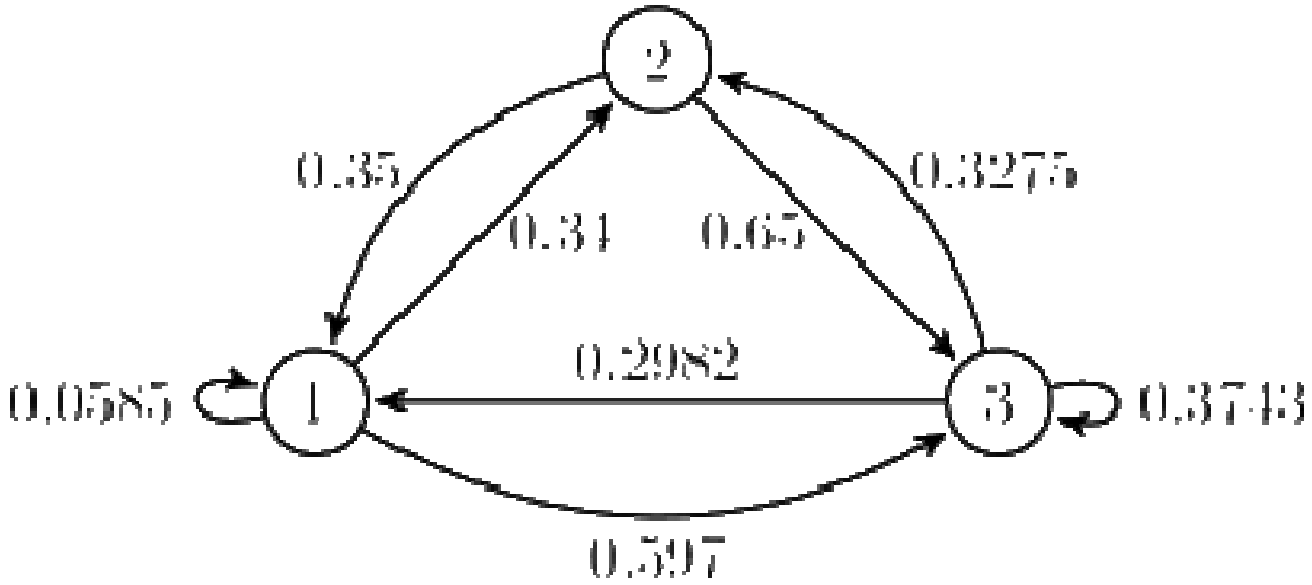

A
Dose
DLT
Non-DLT
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time
B
Dose
DLT
Non-DLT with moderate toxicity
Non-DLT with mild toxicity
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time
C
Dose
DLT and PK threshold reached
Non-DLT and PK threshold reached
Non-DLT and PK threshold not reached
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time
D
Dose
Computation of probabilities of target toxicity and overdosing at next dose level
DLT
Non-DLT
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time

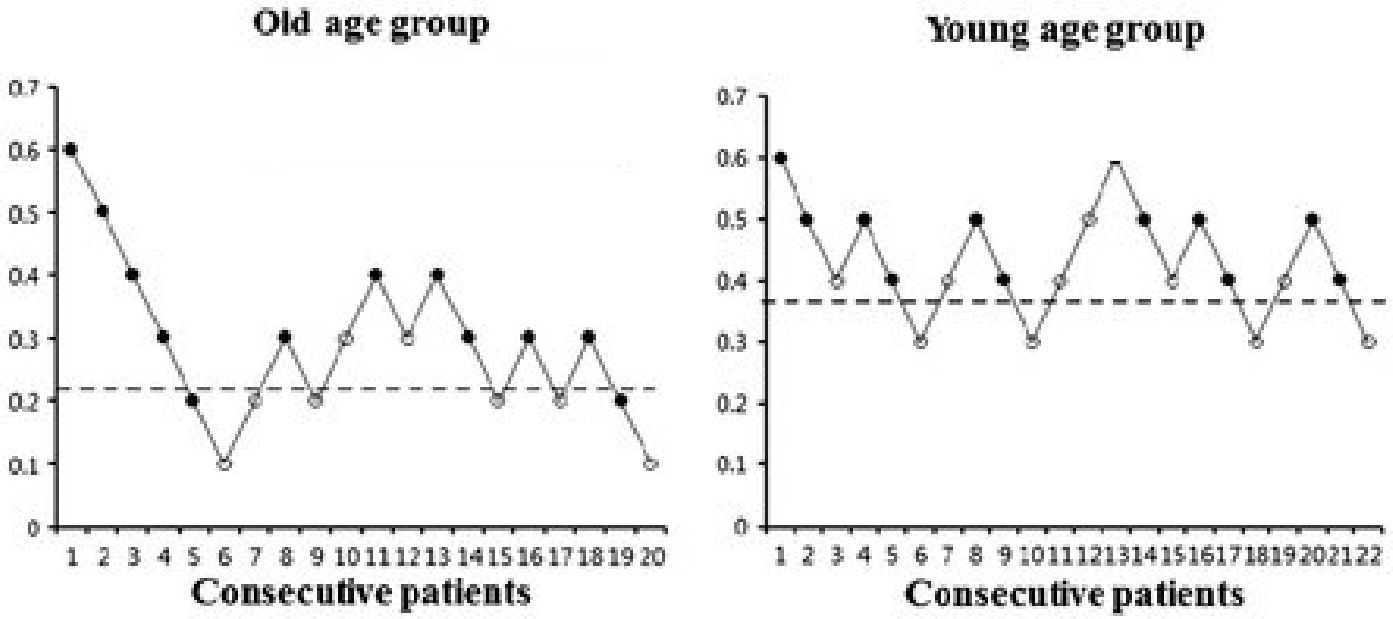
IND or IDE

DTL

MTD

CRM

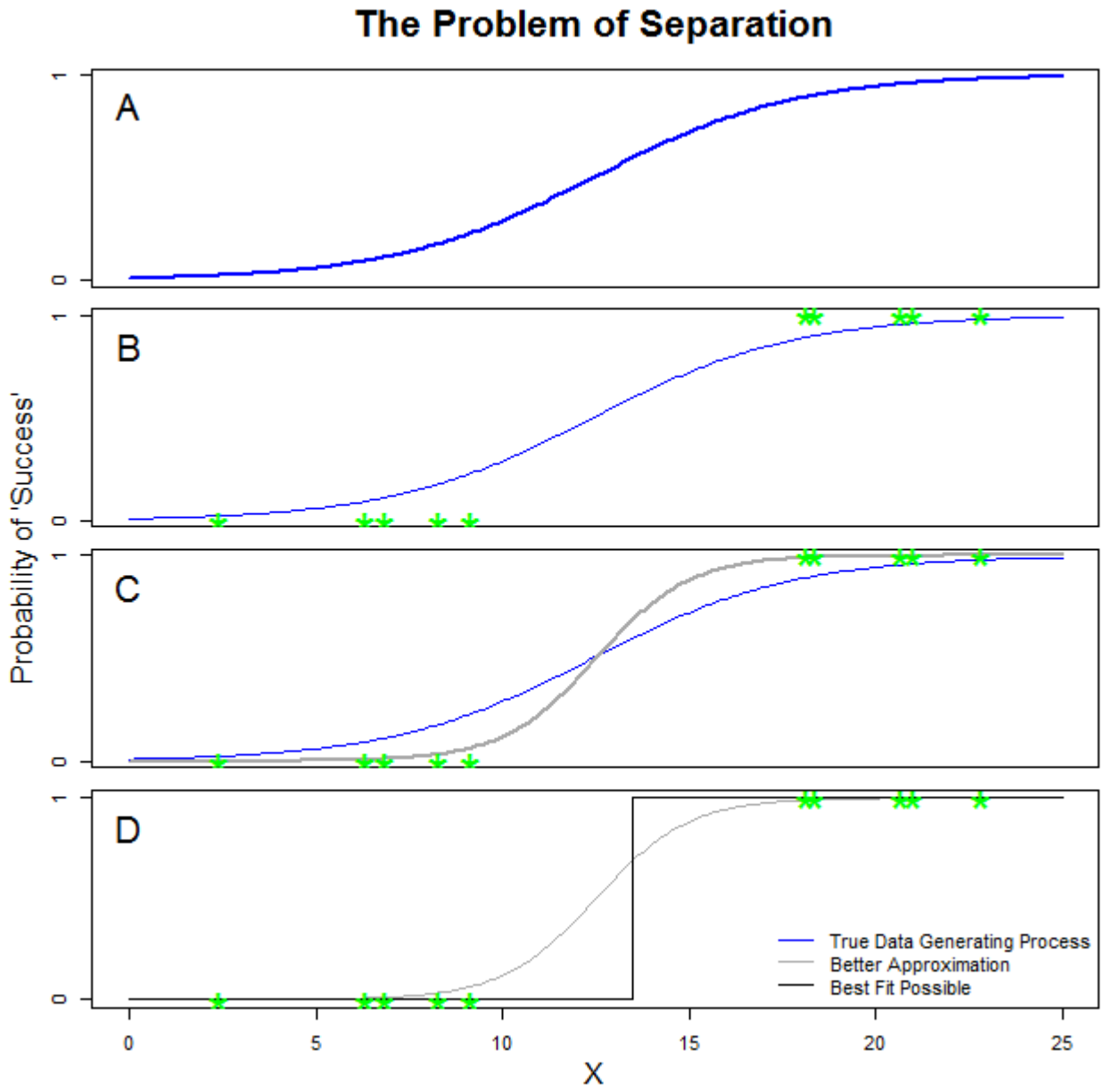

2
0.35
0.34
0.65
0.32756
0.29882
0.05887
1
3
0.37443
0.597

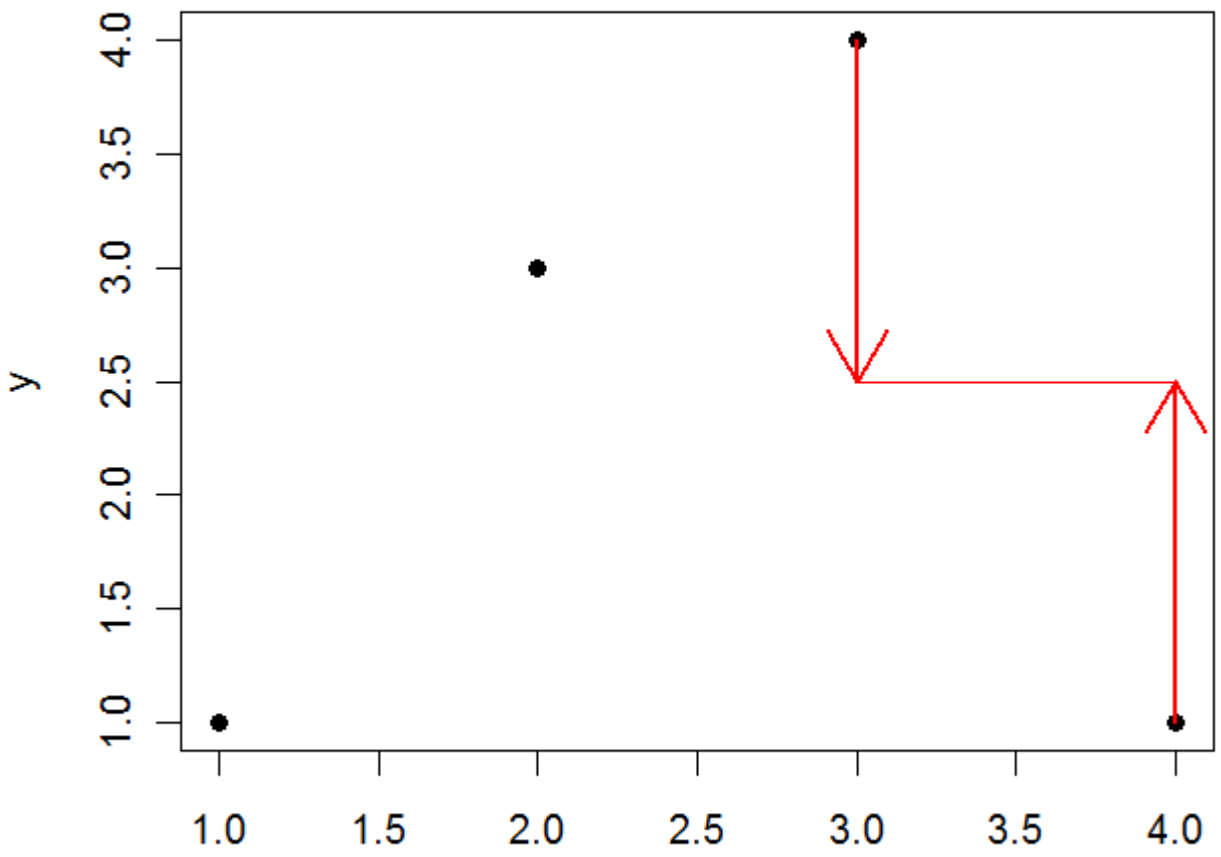


Sedation with single-dose dexmedetomidine in patients undergoing transurethral resection

Drug dose (μg/kg)	Group Y ($n = 22$)	Group O ($n = 20$)
Dixon's method		
ED_{50} (95% C.I.)	0.35 (0.35-0.45)	0.25 (0.15-0.35)
Isotonic regression method		
ED_{50} (83% C.I.)†	0.41 (0.38-0.45)	0.24 (0.19-0.3)
ED_{95} (95% C.I.)‡	0.57 (0.49-0.59)	0.38 (0.29-0.39)

ED_{50}; 50% effective dose, ED_{95}; 95% effective dose, C.I.; confidence interval
Dixon's method *p* value (non-parametric): 0.009.
†Isotonic regression method 83% Confidence interval: do not overlap.
‡Isotonic regression method 95% Confidence interval: do not overlap.


The Problem of Separation
A
B
C
D
Probability of 'Success'
1
0
0
5
10
15
20
25
X
True Data Generating Process
Better Approximation
Best Fit Possible


y
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.0
1.5
2.0
2.5
3.0
3.5
4.0

No. Date :

问题提出.

假定给某种动物服用一种药剂，观察它们是否有阳性反应，剂量分别为 Q_i.

$$Q_1 \le Q_2 \le \cdots \le Q_k \quad \cdots (1)$$

即剂量是逐渐增加的. 对应于剂量 Q_i 实验了 n_i 个动物，用 x_{ij} 来表示这 n_i 个动物中第 j 个动物的反应，$j=1,2,\cdots,n$，$i=1,2,\cdots,k$ 其中

$$x_{ij} = \begin{cases} 1 & \text{有反应} \\ 0 & \text{无反应.} \end{cases}$$

那么有：

i \ j	1	2	$\cdots$	n
Q_1	x_{11}	x_{12}	$\cdots$	x_{1n_1}
Q_2	x_{21}	x_{22}	$\cdots$	x_{2n_2}
$\vdots$		$\cdots$		
Q_k	x_{k1}	x_{k2}	$\cdots$	x_{kn_k}

其中 $n_1, n_2, \cdots n_k \le n$

那么 p_i 表示剂量 Q_i 时有反应的比例，则 $P=(p_1, p_2, \cdots p_k)^T$ 是刻画总体简易的参数，通常用样本比例：来估计 p_i

$$\hat{p}_i = \frac{1}{n_i}\sum_{j=1}^{n_i} x_{ij} \quad \cdots (2)$$

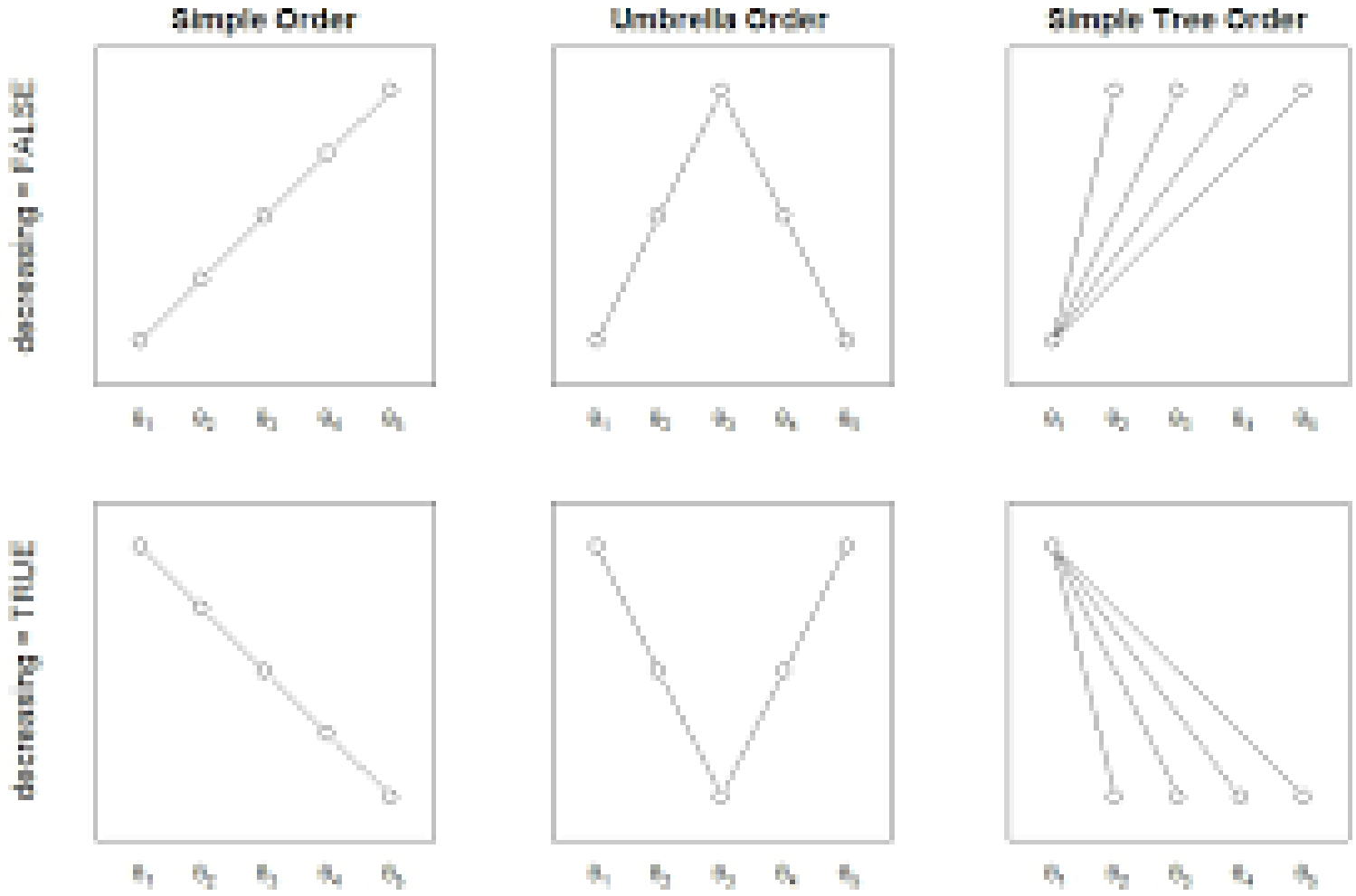
因为 $n_i\hat{p}_i$ 服从二项分布，则似然函数为：$\prod_{i=1}^{k} p_i^{n_i\hat{p}_i}(1-p_i)^{n_i(1-\hat{p}_i)} = L$

那么 $\ln(L) = \sum_{i=1}^{k} n_i\hat{p}_i \ln(p_i) + n_i(1-\hat{p}_i)\cdot\ln(1-p_i)$

对 p_i 求导：$\frac{\partial \ln(L)}{p_i} = \frac{n_i\hat{p}_i}{p_i} - \frac{n_i(1-\hat{p}_i)}{(1-p_i)}$ 让其等于 0

则 $\hat{p}_i = p_i$

这时 P 的最大似然估计，记为 (1) 的约束下，L 取得最大值


Simple Order
Umbrella Order
Simple Tree Order
decreasing = FALSE
decreasing = TRUE

When will you use CRM and when the 3+3?

Do we need to specify the total sample size for the 3+3 design? For the CRM?

How to determine the total sample size for the CRM?

Can we approximate the whole dose-toxicity curve with the CRM?

The 3+3 design and the CRM are not used in phase 1 studies with healthy volunteers. Why?

Are isotonic estimates MLEs?