Statistical Innovations in Dose-Finding and Dose Optimization in Oncology

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Course Overview

Lesson 1: Dose Finding in Phase I trials

- Why Phase I?
- Dose escalation methods (BOIN)

Lesson 2: Dose Finding in Phase II trials

- Beyond MTD
- Why Phase II?
- Introduction to MCP-Mod

Lesson 3: Practical

- Dose-response analysis of a continuous endpoint
- Dose-response analysis of a binary outcome
- Further exercise and group work

SYMSTAT 2025 - talk

- Bayesian variable selection method for dose-response analysis

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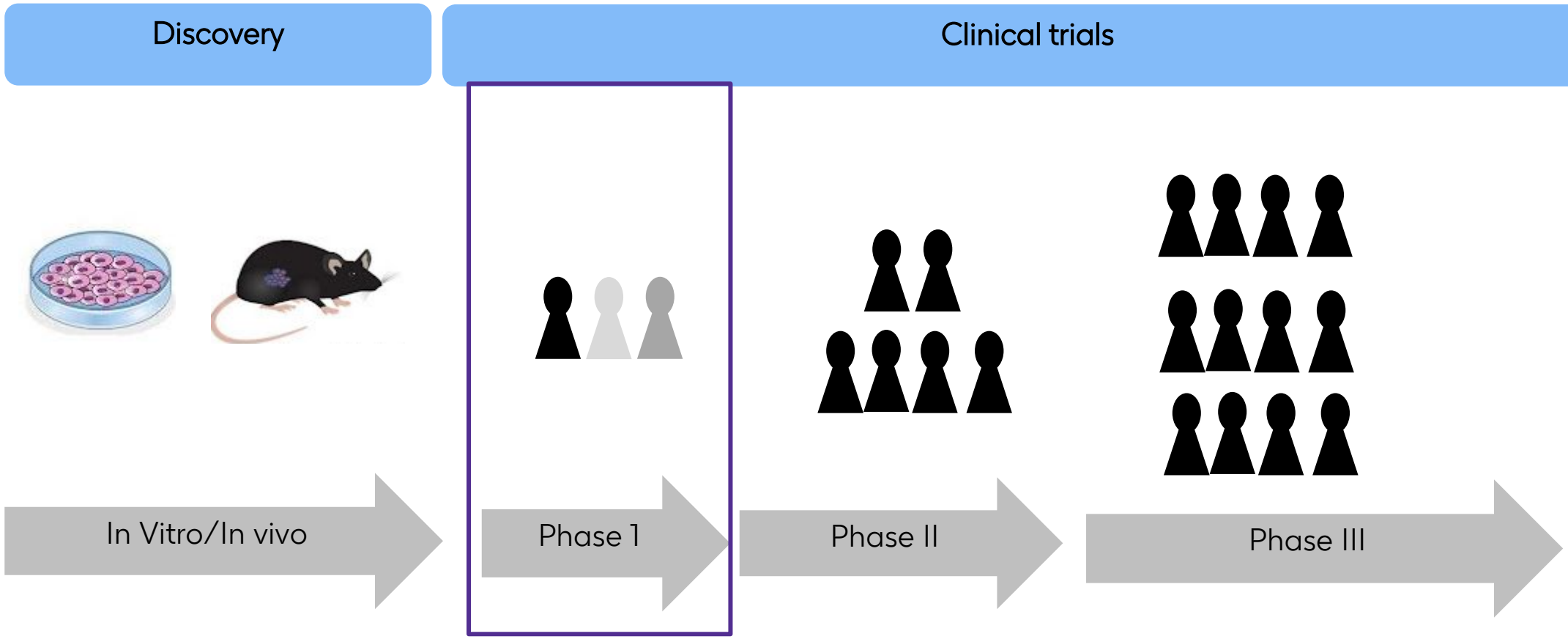
Dose Finding in Phase I Trials

Objective and Learning Outcomes

- **Objective**
  - Introduce methods for dose-escalation studies in phase I oncology trials
- **Learning Outcomes**
  - Understand rationale for phase I trial
  - Conceptual understating of BOIN method
  - Design a phase I trial using BOIN method.

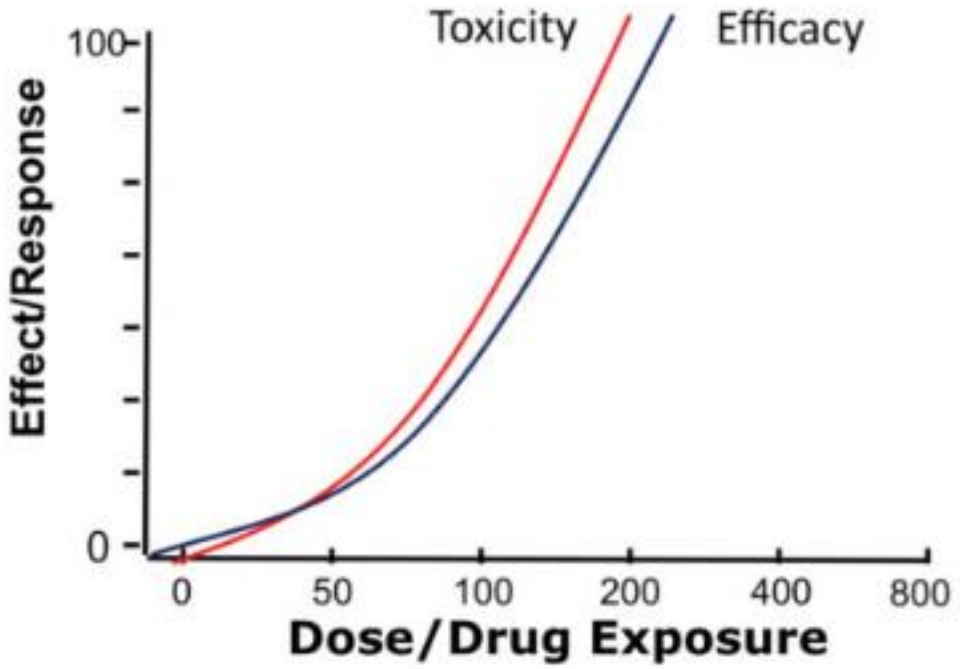
Drug Development

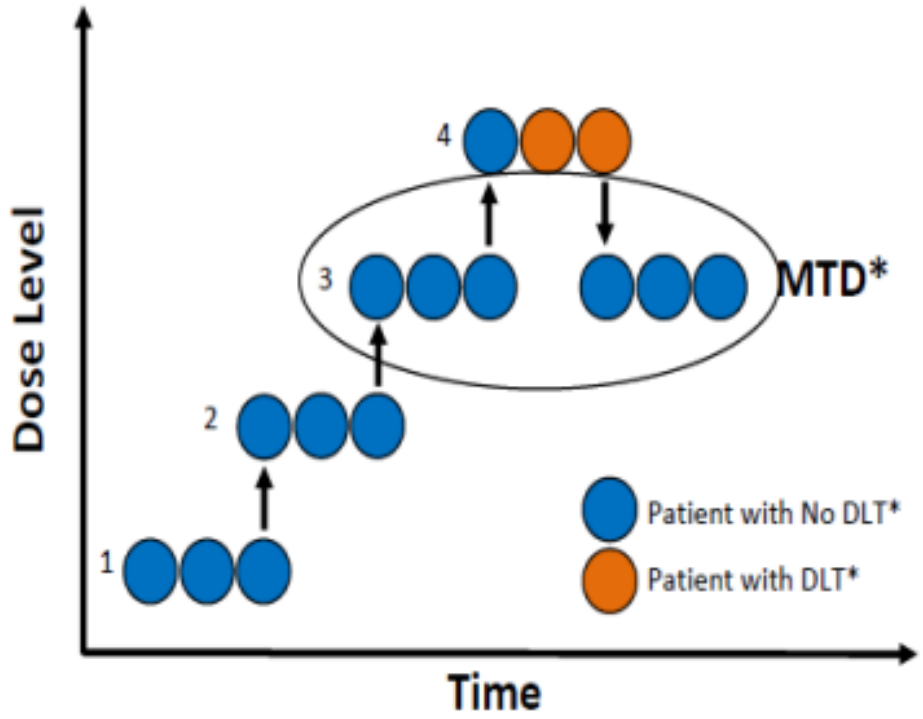


Phase 1 trial

Purpose	Description
Safety evaluation	Determine the appropriate dosing levels by identifying the maximum tolerated dose (MTD). This involves administering the drug at gradually increasing doses while closely monitoring patients for adverse effects.
Pharmacokinetics	Absorption, Distribution, Metabolism, and Excretion (ADME): Phase I studies investigate how the body absorbs, distributes, metabolizes, and excretes the drug. This informs optimal dosing schedules.
Pharmacodynamics	Understanding how the drug interacts at the cellular and molecular levels within the human body, including its effects on tumors.
Initial efficacy signals	Although Phase I trials focus primarily on safety, they may provide preliminary data regarding potential therapeutic benefits, such as tumor shrinkage or biomarker changes.

Maximum tolerated dose - MTD



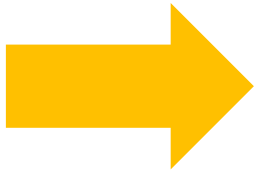


Traditionally, it is aimed to find the maximum tolerated dose under the assumption that toxicity and efficacy increase with an increase in dose. Dose limiting toxicity (DLT) is observed within a defined window, typically 1 or 2 cycles of treatment. A treatment cycle is defined by the project team.

Dose recommendations

Dose escalation in phase I studies are broadly guided by three statistical recommendations

Escalate to a higher dose if no DLT observed



Stay/Remain if there is a minor safety concern

De-escalate or terminate if DLT is observed in multiple patients

Dose escalation methods

Rule-based

3+3 design, rolling-six.

- Targets **observed** toxicity rate of 33%
- Simple but rigid, inefficient at finding the MTD

Model-based

CRM, EWOC, BLRM

- 1 or 2 parameter model
- Targets highest dose with Prob(DLT rate) <= Φ (typically 25-30%)
- Next dose is dose with highest posterior probability of being near the target

Model-informed

BOIN, mTPI, mTPI-2

- simplicity of algorithmic designs with efficiency of model-based designs
- Targets highest dose with Prob(DLT)<= Φ(typically 25-30%)
- Decision can be pre-tabulated

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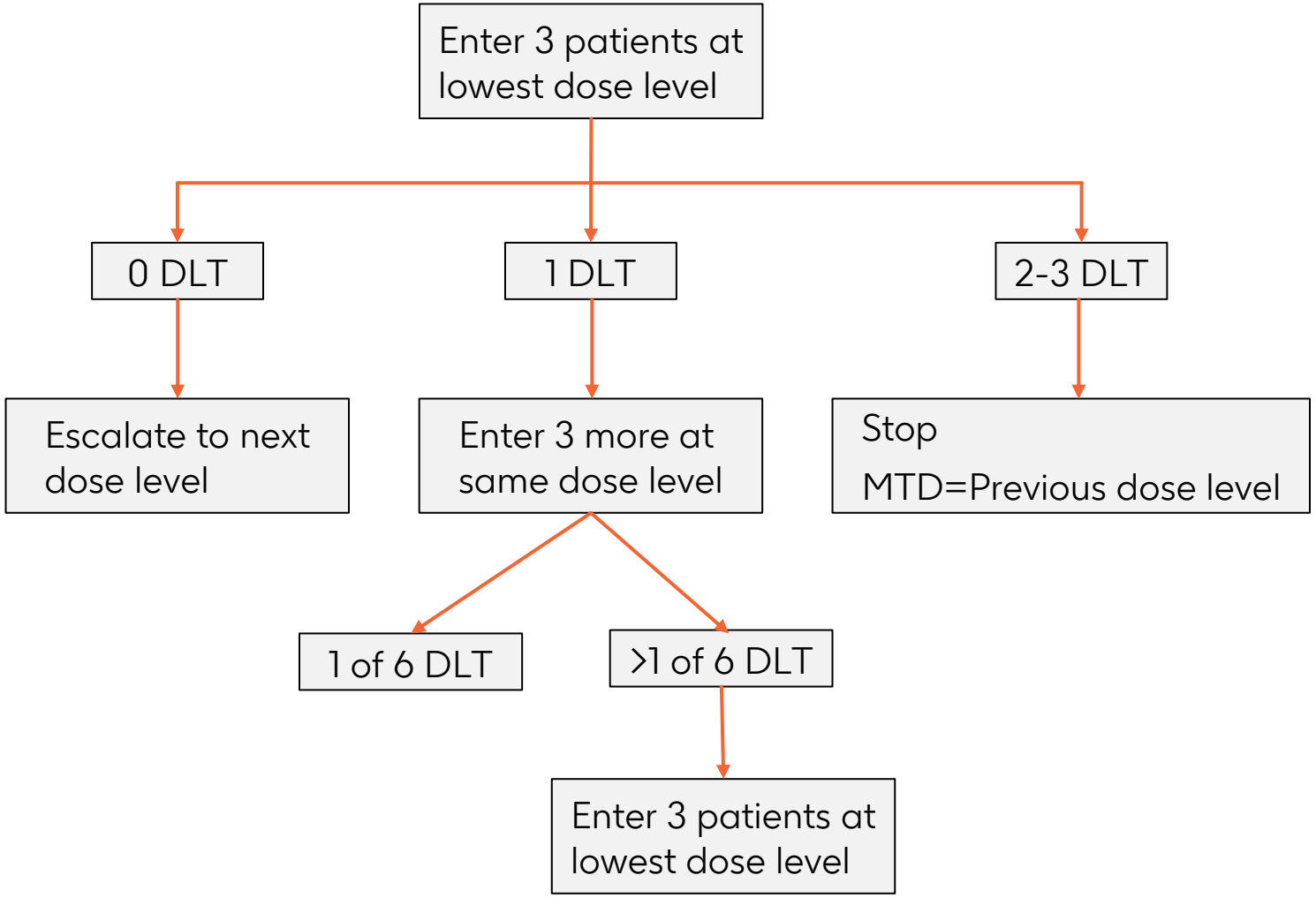
3+3 Design

A 3+3 design is a deterministic rule-based design. It is known to be a rigid and inefficient, with least statistically desirable operating characteristics



Bayes' Theorem

An innovation in dose escalation method is the adoption of Bayesian framework to update the chance of toxicity based on prior belief. At the core of a Bayesian method is the Bayes' theorem that combines prior probability with the likelihood from the data. Supposed A is a hypothesis and B is the prior evidence;

$$P(A|B) = \frac{P(B|A) * P(A)}{P(B)}$$

- The prior probability of the hypothesis - $P(A)$
- The likelihood of observing the evidence given the hypothesis - $P(B|A)$
- The prior probability of the evidence - $P(B)$

Posterior Probability

Question

What is the probability that one patient out of 6 will experience a DLT given the prior belief of 5% chance of toxicity?

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Posterior Probability

Posterior = Data + Prior belief

Solution

- The prior belief can be expressed in terms of a Beta distribution $Be\ (\alpha_0, \beta_0)$, where α_0 and β_0 are the shape parameters
- The likelihood is from a Binomial distribution $B(p, n)$, where p is the probability of a DLT and n is the total number of patients
- The posterior is a Beta distribution- $Be(\alpha_0 + x, \beta_0 + n - x)$. Where x is the number of patients with DLT.

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Prior & Posterior Probabilities

Posterior = Data + Prior belief

Solution

- The probability that x patient out of n will experience a DLT given the prior distribution $Be\ (\alpha_0, \beta_0)$ can be calculated as

$$\frac{\alpha_0 + x}{\alpha_0 + x + \beta_0 + n - x} = \frac{\alpha_0 + x}{\alpha_0 + \beta_0 + n}$$

- Supposed the prior belief is represented by $Be\ (0.05, 0.95)$, such that the prior effective sample size is 1. Then the probability of 1 out of 6 patient with a DLT is **15%**

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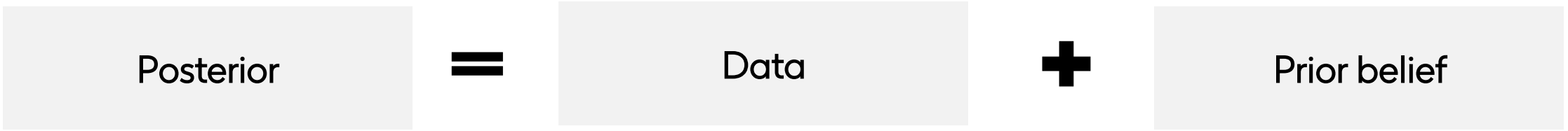
Exercise 1



Question

Assuming the prior belief of 15% toxicity that is defined by Be(0.15,0.85), what is the probability that 1 out of 3 patients would have a DLT?

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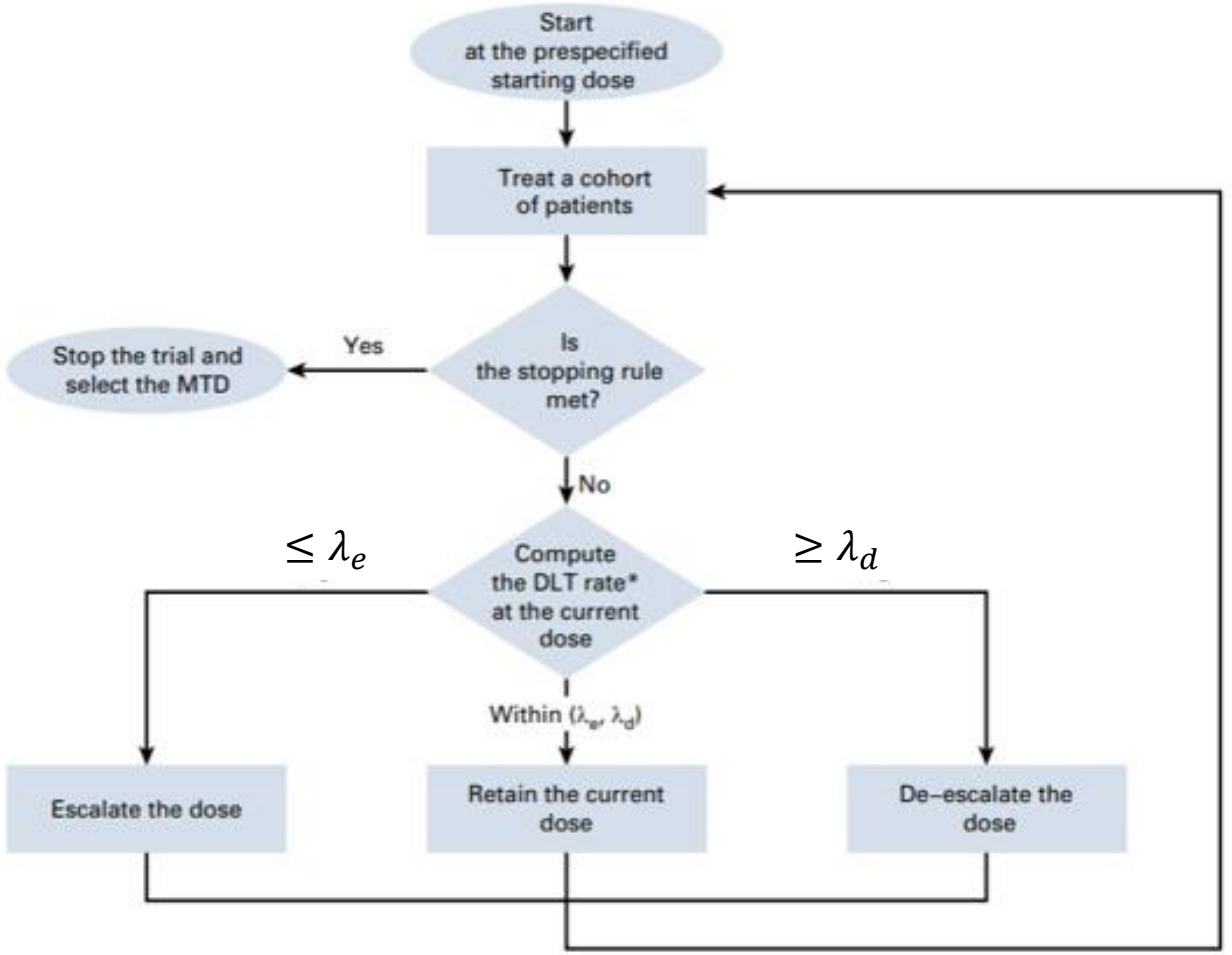
Bayesian Optimal Interval Design - BOIN

There are several Bayesian methods for dose-escalation studies, including the Bayesian Logistic regression model (BLRM). In this course, we would focus on BOIN method.

- Target toxicity rate (p) at the maximum tolerated dose (MTD)
- The boundary value (λ_e) to indicate subtherapeutic dosage
- The boundary value (λ_d) to indicate overdosing



Bayesian Optimal Interval Design - BOIN

To determine the boundary values, the method minimizes the likelihood of incorrect decision based on the three heuristic hypotheses. Let p_j denotes the true toxicity probability of dose level j. The three hypotheses are

Hypothesis	Correct Decision	Incorrect Decision
$H_1: p_j = \phi$	Retainment (R)	Escalation or De-escalation $(\bar{R})$
$H_2: p_j = \phi_1$	Escalation (E)	De-escalation $(\bar{E})$
$H_3: p_j = \phi_2$	De-escalation (D)	Escalation $(\bar{D})$

- ϕ denotes the probability at the MTD
- ϕ_1 denotes the highest toxicity probability that is deemed subtherapeutic (i.e below the MTD)
- ϕ_2 denotes the lowest toxicity probability that is deemed overly toxic (i.e above the MTD)

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Bayesian Optimal Interval Design - BOIN

Let the probability of making an incorrect decision (the decision error rate), denoted as $\alpha(\lambda_{1j}, \lambda_{2j})$. Determine the values of λ_{1j} and λ_{2j} that minimize the probability of incorrect decision.

$$\alpha(\lambda_{1j}, \lambda_{2j}) = \mathrm{pr}(H_{oj})\mathrm{pr}(\bar{R}|H_{oj}) + \mathrm{pr}(H_{1j})\mathrm{pr}(\bar{E}|H_{oj}) + \mathrm{pr}(H_{2j})\mathrm{pr}(\bar{D}|H_{oj})$$

$$\mathrm{pr}(\bar{R}|H_{oj}) = pr(m_j < n_j\lambda_{1j}) + pr(m_j > n_j\lambda_{2j})$$

$$\mathrm{pr}(\bar{R}|H_{oj}) = B(n_j\lambda_{1j}; n_j, \phi) + 1 - B(n_j\lambda_{2j} - 1; n_j, \phi)$$

- $B(b; n, \phi)$ is cumulative density function of the binomial distribution with size n and probability ϕ, evaluated the value b

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Bayesian Optimal Interval Design - BOIN

Similarly,

$$\alpha(\lambda_{1j}, \lambda_{2j}) = \text{pr}(H_{oj})\text{pr}(\bar{R}|H_{oj}) + \text{pr}(H_{1j})\text{pr}(\bar{E}|H_{1j}) + \text{pr}(H_{2j})\text{pr}(\bar{D}|H_{2j})$$

$$\text{pr}(\bar{E}|H_{1j}) = 1 - B(n_j\lambda_{1j} - 1; n_j, \phi_1)$$

$$\text{pr}(\bar{D}|H_{2j}) = B(n_j\lambda_{2j} - 1; n_j, \phi_2)$$

- $\text{pr}(H_{oj})$, $\text{pr}(H_{1j})$ and $\text{pr}(H_{2j})$ are equal prior probabilities i.e non informative priors

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Bayesian Optimal Interval Design - BOIN

The decision error is minimum when,

$$\lambda_{ij} = log\frac{1-\phi_1}{1-\phi} / log\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}$$

$$\lambda_{2j} = log\frac{1-\phi}{1-\phi_2} / log\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}$$

Exercise 2

Complete the table below assuming $\phi_1 = 0.6\phi$ and $\phi_2 = 1.2\phi$

Boundary	Target toxicity rate for MTD (ϕ)			
	0.15	0.2	0.3	0.4
λ_{ij}				
λ_{2j}				

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Generalisation

- Boundary values obtained under the non-informative priors are invariant to dose levels
- Practical implementations require that the boundary values are independent of dose levels and can be pre-tabulated.
- The generalisation from dose levels specific boundary values require formulating composite hypothesis and working with a Beta distribution instead of binomial distribution
- **For further reading about BOIN method and its generalization, read Liu S and Yuan Y paper Bayesian optimal interval designs for phase I clinical trials. J R Stat Soc Ser C Appl Stat 2015;64:507–23.**

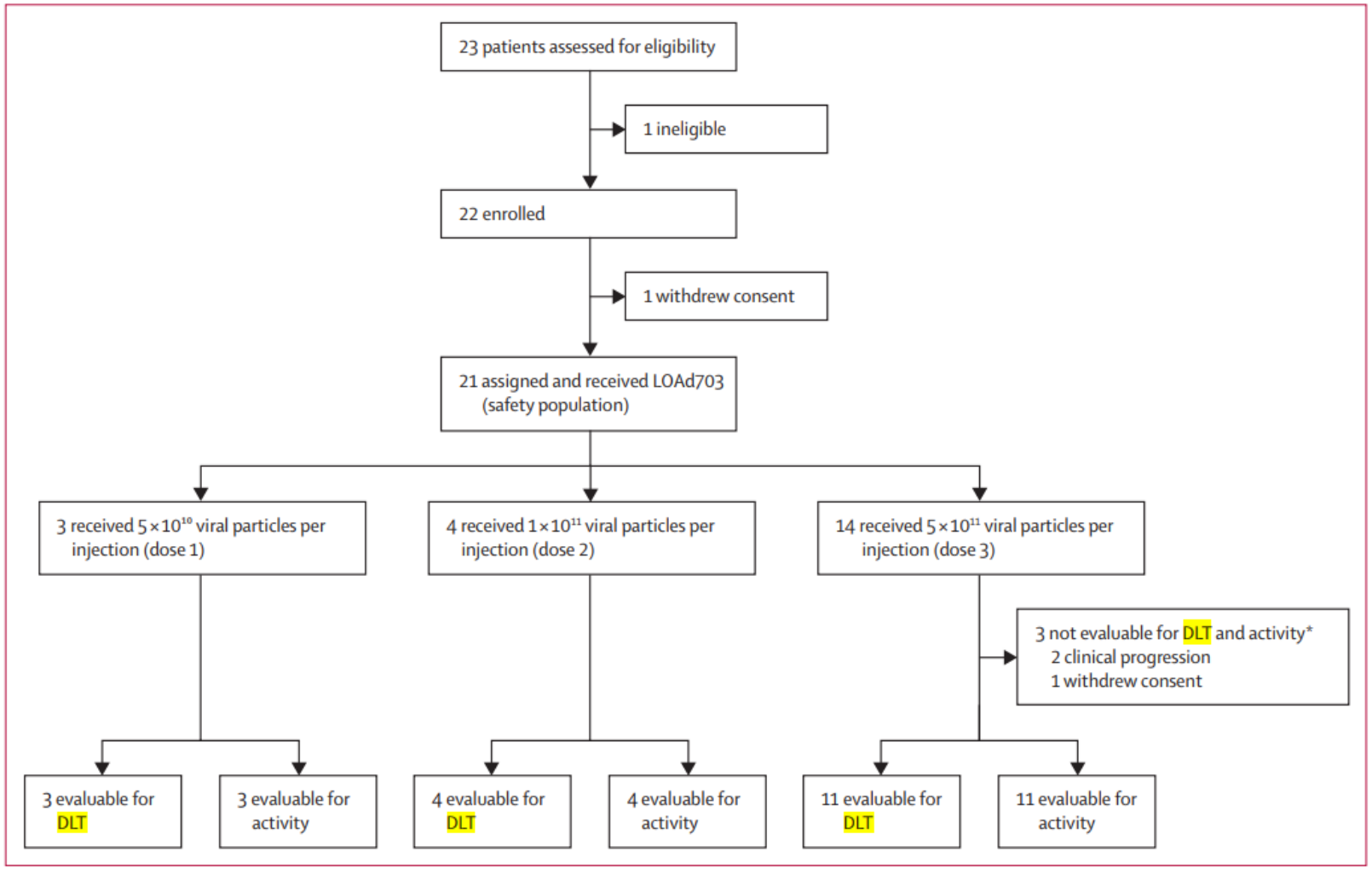
Case Study

LOAd703, an oncolytic virus-based immunostimulatory gene therapy, combined with chemotherapy for unresectable or metastatic pancreatic cancer (LOKON001): results from arm 1 of a non-randomised, single-centre, phase 1/2 study

- Musher *et al* (2024)

Case Study

Study conducted between Dec 2, 2016, and Oct 17, 2019



Case Study

Use BOIN method to determine the MTD dose for a hypothetical phase I trial of LOAd703 based on the following assumptions and DLT data

Assumptions

- 3 Dose Levels; Dose 1, Dose2 and 3
- 3, 4, and 11 patients per dose, respectively
- Targeted toxicity rate of 30% at MTD

Case Study

Use BOIN method to determine the MTD dose for a hypothetical phase I trial of LOAd703 based on the following assumptions and DLT data

DLT Data: number of patients with DLT per cohort

	Dose 1	Dose 2	Dose 3			
	Cohort 1 N=3	Cohort 2 N=4	Cohort 3 N=3	Cohort 4 N=3	Cohort 5 N=3	Cohort 6 N=2
Scenario 1	0	0	0	1	0	0
Scenario 2	0	1	0	1	1	1
Scenario 3	0	1	1	0	1	1

Case Study

```
# Load necessary library

if (!require(BOIN)) {  install.packages("BOIN")}

library(BOIN)

#Get Boundary

bound  <-  get.boundary(target=0.3, ncohort=18, cohortsize=3)
```

Case Study

- Pre-tabulated decision table.

Number of patients treated	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Escalate if # of DLT <=	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4
Deescalate if # of DLT >=	1	1	2	2	2	3	3	3	4	4	4	5	5	6	6	6	7	7
Eliminate if # of DLT >=	NA	NA	3	3	4	4	5	5	5	6	6	7	7	8	8	8	9	9

- The boundary values the error functions are λ_1=0.236 and λ_2= 0.359

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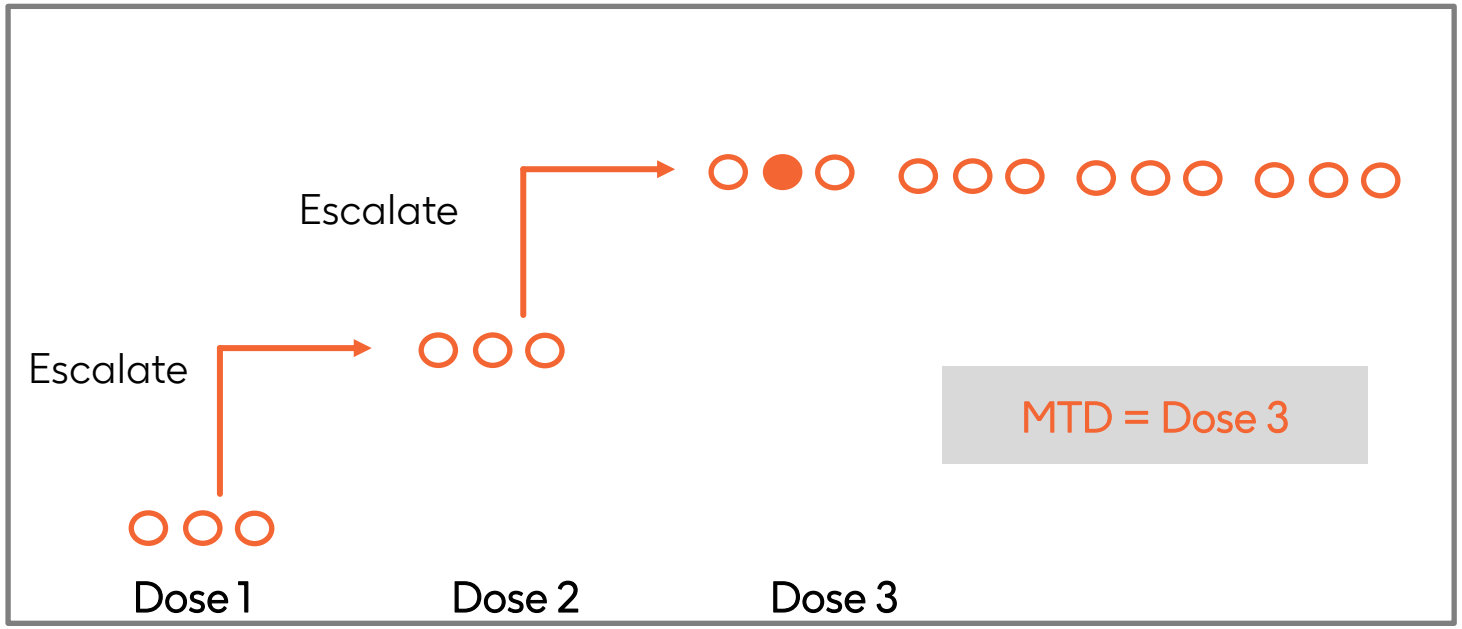
Scenario 1

Dose recommendation under scenario 1



Scenario 1

```
## create data
patients <- c(3, 4,11)  ## number of patients per dose
dlt <- c(0, 0,1)                ## number of dlt per dose

## determine the MTD
selmtd <- select.mtd(target=0.3, npts=patients, ntox=dlt)
```

```
> summary(selmtd)
The MTD is dose level  3
```

Dose Level	Posterior DLT Estimate	95% Credible Interval	Pr(toxicity>0.3|data)
1	0.01	(0.00,0.16)	0.01
2	0.01	(0.00,0.16)	0.01
3	0.09	(0.00,0.31)	0.03

NOTE: no estimate is provided for the doses at which no patient was treated.

Exercise 3

Determine the MTD for scenario 2 & 3 and provide justification for your dose recommendation.

DLT Data: number of patients with DLT per cohort

	Dose 1	Dose 2	Dose 3			
	Cohort 1 N=3	Cohort 2 N=4	Cohort 3 N=3	Cohort 4 N=3	Cohort 5 N=3	Cohort 6 N=2
Scenario 2	0	1	0	1	1	1
Scenario 3	0	1	1	0	1	1

Operating characteristics

We have assumed until now that a dose-escalation study has been conducted and the DLT data is available for analysis. However, Statisticians mostly rely on simulation studies to inform study design because data from the trial are not available at this stage.

Key Questions

- What is the expected toxicity at MTD?
- What are the like toxicity level per dose?
- How many patient is needed?

Operating Characteristics

- What is the total number of DLT and average DLT per dose?
- How many patients allocated to the MTD?
- What is the impact of starting dose?
- …

Operating characteristics

Design a hypothetical dose escalation study assuming 20% target toxicity at MTD , a total sample size of 36 patients with 3 patients per cohort and different starting dose levels (Dose 1, Dose 2 and Dose 3). Derive the operating characteristic with and without early stopping after 9 patient has been assigned to the MTD.

The true toxicity rate per dose are:

Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
0.02	0.05	0.08	0.1	0.15

Scenario 1: Starting Dose = Dose 1

Simulation Set up

```
target  = 0.25            # target toxicity at MTD
p.true =  c(0.02,0.05,0.08,0.1,0.15) # True toxicity level per dose
ncohort  = 12    # total number of cohorts
cohortsize = 3 ## number of patients per cohort
Startdose =1 # starting dose
Ntrial =1000 ## number of simulated trials
seed=6  ## simulation seed to ensure reproducibility
```

Simulation Code

```
scen1_Dose1 <- get.oc(target, p.true, ncohort,
                      cohortsize,      startdose,
                      ntrial=1000,  seed=6)
```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Scenario 1: Starting Dose = Dose 1

Results

```
$ simu.setup :'data.frame':                5 obs. of  12 variables:
  ..$ target    : num [1:5] 0.25 0.25 0.25 0.25 0.25
  ..$ p.true    : num [1:5] 0.02 0.05 0.08 0.1 0.15
  ..$ ncohort   : num [1:5] 12 12 12 12 12
  ..$ cohortsize: num [1:5] 3 3 3 3 3
  ..$ startdose : num [1:5] 1 1 1 1 1
  ..$ p.saf     : num [1:5] 0.15 0.15 0.15 0.15 0.15
  ..$ p.tox     : num [1:5] 0.35 0.35 0.35 0.35 0.35
  ..$ cutoff.eli: num [1:5] 0.95 0.95 0.95 0.95 0.95
  ..$ extrasafe : logi [1:5] FALSE FALSE FALSE FALSE FALSE
  ..$ offset    : num [1:5] 0.05 0.05 0.05 0.05 0.05
  ..$ ntrial    : num [1:5] 1000 1000 1000 1000 1000
  ..$ dose      : int [1:5] 1 2 3 4 5
$ selpercent : num [1:5] 0.1 0.5 2.4 9.7 87.3
 $ npatients  : num [1:5] 3.74 4.58 5.39 6.59 15.7
 $ ntox       : num [1:5] 0.071 0.221 0.405 0.632 2.381
 $ totaltox   : num 3.71
 $ totaln     : num 36
 $ percentstop: num 0
 $ flowchart  : logi TRUE
 $ lambda_e   : num 0.197
 $ lambda_d   : num 0.298
 - attr(*, "class")= chr "boin"
```


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Scenario 1: Starting Dose = Dose 1

Operating Characteristics

- The most selected dose as MTD is Dose 5
- Only 44% of the patients were treated at MTD
- 56% of the patients were treated at a sub-therapeutic dose
- Average toxicity is about 4 out of **36**

Dose	Target	P.True	selpercent	#patients	#tox
1	0.25	0.02	0.1	3.738	0.071
2	0.25	0.05	0.5	4.578	0.221
3	0.25	0.08	2.4	5.388	0.405
4	0.25	0.1	9.7	6.594	0.632
5	0.25	0.15	87.3	15.702	2.381

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Scenario 1: Starting Dose = Dose 2

Simulation Set up

target = 0.25 # target toxicity at MTD

p.true = c(0.02,0.05,0.08,0.1,0.15) # True toxicity level per dose

ncohort = 12 # total number of cohorts

cohortsize = 3 ## number of patients per cohort

Startdose =2 # starting dose

Ntrial =1000 ## number of simulated trials

seed=6 ## simulation seed to ensure reproducibility

Operating Characteristics

Dose	Target	P.True	selpercent	#patients	#tox
1	0.25	0.02	0	0.495	0.009
2	0.25	0.05	0.2	4.629	0.213
3	0.25	0.08	2.2	5.616	0.446
4	0.25	0.1	8.9	6.912	0.695
5	0.25	0.15	88.7	18.348	2.757

- The most selected dose as MTD is Dose 5
- Only 50% of the patients were treated at MTD
- 50 % of the patients were treated at a sub-therapeutic dose
- Dose 1 – Dose were selected as MTD < 1%
- Average toxicity is about 4 out of 36

Scenario 1: Starting Dose = Dose 3

Simulation Set up

```
target  = 0.25            # target toxicity at MTD
p.true =  c(0.02,0.05,0.08,0.1,0.15) # True toxicity level per dose
ncohort  = 12    # total number of cohorts
cohortsize = 3 ## number of patients per cohort
Startdose =2 # starting dose
Ntrial =1000 ## number of simulated trials
seed=6  ## simulation seed to ensure reproducibility
```

Operating Characteristics

Dose	Target	P.True	selpercent	#patients	#tox
1	0.25	0.02	0	0.135	0.006
2	0.25	0.05	0.3	1.101	0.055
3	0.25	0.08	1.5	5.658	0.435
4	0.25	0.1	7.4	7.167	0.715
5	0.25	0.15	90.8	21.939	3.264

- The most selected dose as MTD is Dose 5
- Only 58% of the patients were treated at MTD
- 42 % of the patients were treated at a sub-therapeutic dose
- Dose 1 – Dose were selected as MTD < 1%
- Average toxicity is about 4.5 out of 36

Scenario 1: Impact of Early Stopping

- The previous design assigned most patients to Dose 5, which may be desirable since it provides more data on the potential recommended Phase 2 dose (RP2D). However, it takes longer to completed the study.
- To move faster and to reduce cost, early stopping may be consider to stop dose-escalation after a fixed number of patients have administered the same dose.

Starting Dose = 2 with an early stopping of 9 patients

Dose	Target	P.True	selpercent	#patients	#tox
1	0.25	0.02	0.2	0.549	0.014
2	0.25	0.05	3.8	4.425	0.215
3	0.25	0.08	8.5	4.839	0.409
4	0.25	0.1	12.3	5.649	0.531
5	0.25	0.15	75.2	7.455	1.147

Starting Dose = 3 with an early stopping of 9 patients

Dose	Target	P.True	selpercent	#patients	#tox
1	0.25	0.02	0.2	0.144	0.007
2	0.25	0.05	1.2	1.113	0.063
3	0.25	0.08	8.4	4.974	0.401
4	0.25	0.1	11.7	5.679	0.557
5	0.25	0.15	78.5	7.734	1.13

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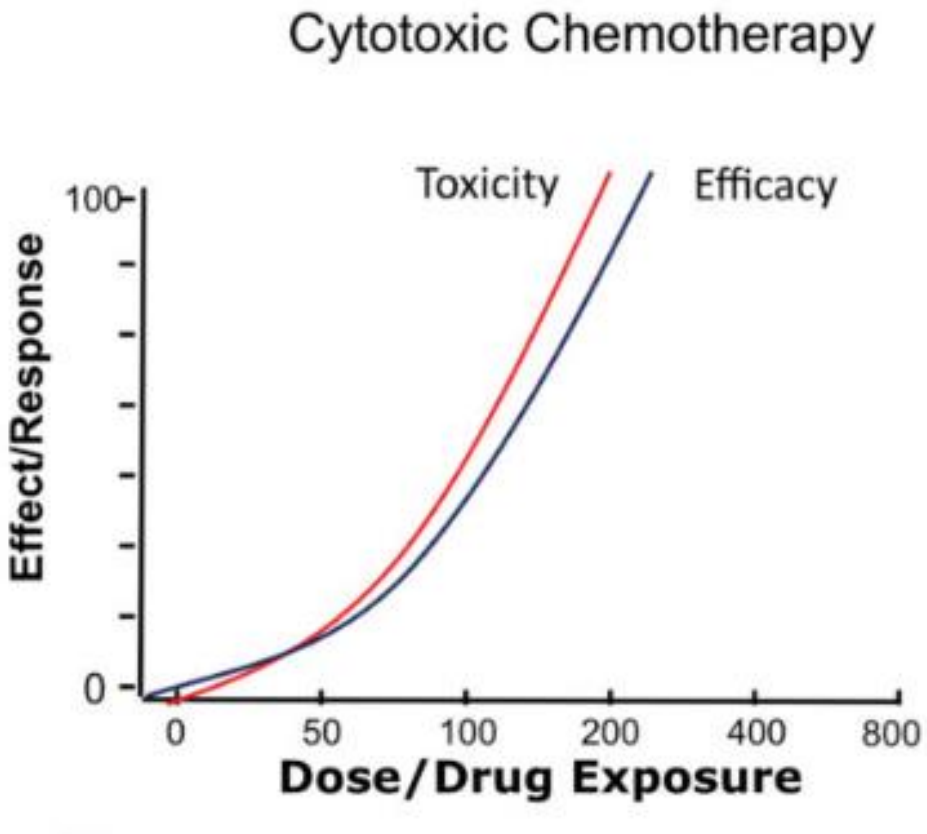
Group work 1

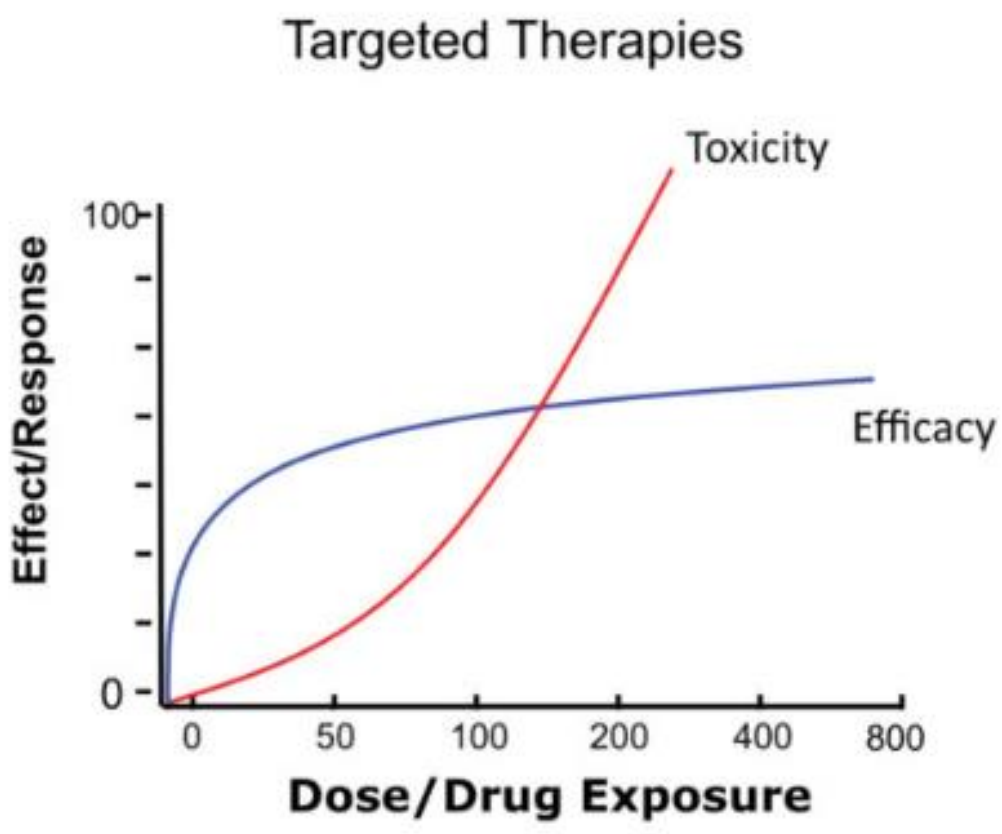
Design a hypothetical dose escalation study assuming 20% target toxicity at MTD , a total sample size of 36 patients with 3 patients per cohort and different starting dose (Dose 1, Dose 2 and Dose 3). Derive the operating characteristic for your design with and without early stopping after 9 patient has been assign to the MTD.

Scenario	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
1	0.10	0.2	0.25	0.30	0.35
2	0.05	0.10	0.20	0.35	0.30
3	0.25	0.30	0.35	0.40	0.35

Beyond MTD

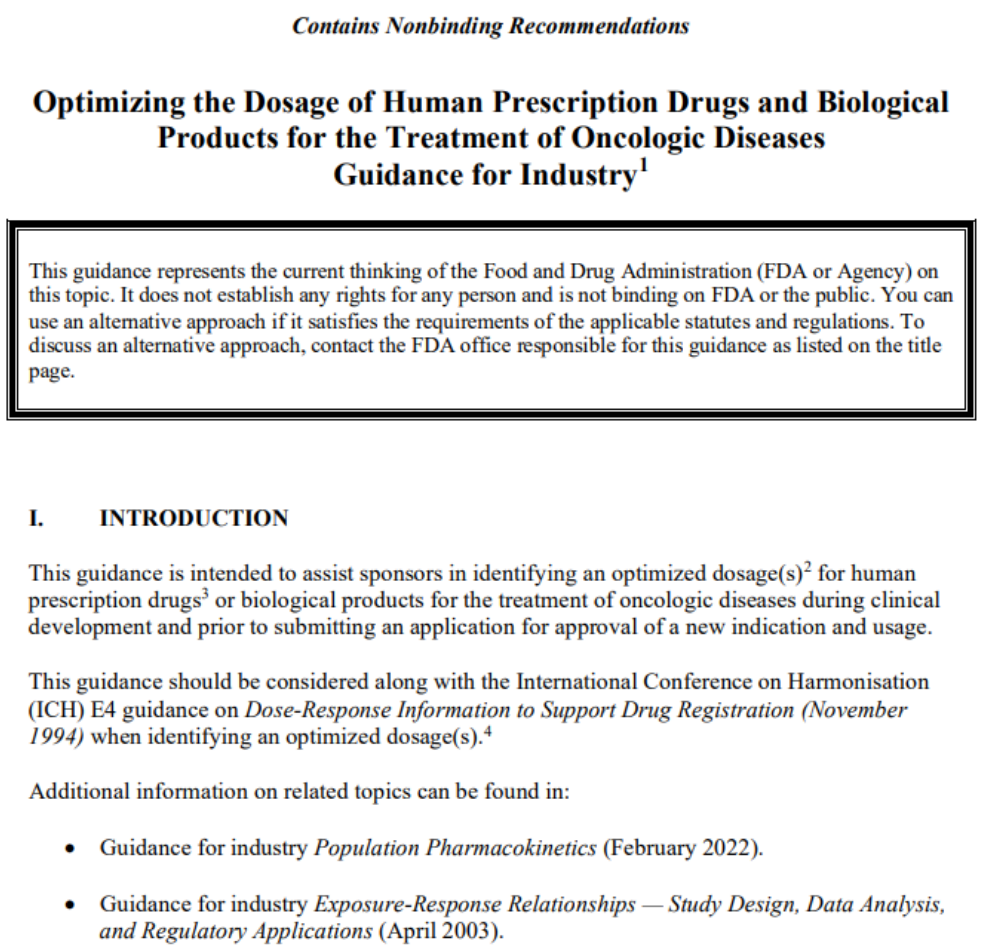
Phase I – Molecular Targeted Agents & Immunotherapies





Is “more” always better?

FDA's Project optimus: Reform dose optimisation for oncology



Contains Nonbinding Recommendations

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases
Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors in identifying an optimized dosage(s)[2] for human prescription drugs[3] or biological products for the treatment of oncologic diseases during clinical development and prior to submitting an application for approval of a new indication and usage.

This guidance should be considered along with the International Conference on Harmonisation (ICH) E4 guidance on *Dose-Response Information to Support Drug Registration (November 1994)* when identifying an optimized dosage(s).[4]

Additional information on related topics can be found in:

- Guidance for industry *Population Pharmacokinetics* (February 2022).
- Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003).

Sort out dosing designs *before* approval

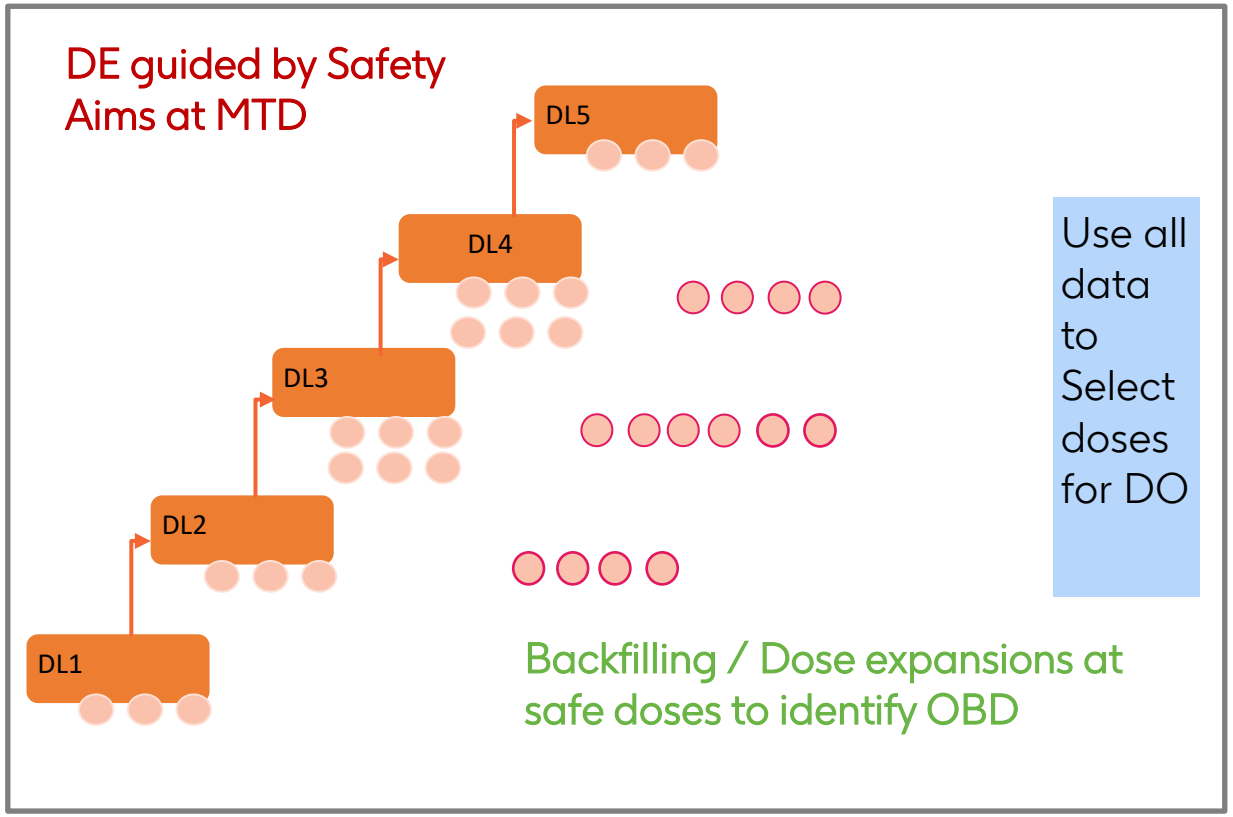
1. **Characterize human biological dosage** (preclinical dose-exposure relationship)
2. Understand and characterize the dose-response relationship for toxicity and for activity
3. Consider all data beyond DLT to identify a target dose range of interest (overall toxicity profile over prolonged period of time, efficacy data short & long term, PROs, Modelling etc..)
4. Conduct **randomized dose-optimisation (DO) trials with min 2 doses** to confirm efficacy and safety at well informed doses (phase II)

Identify "optimal dose" for further study
(indication specific / combination specific)

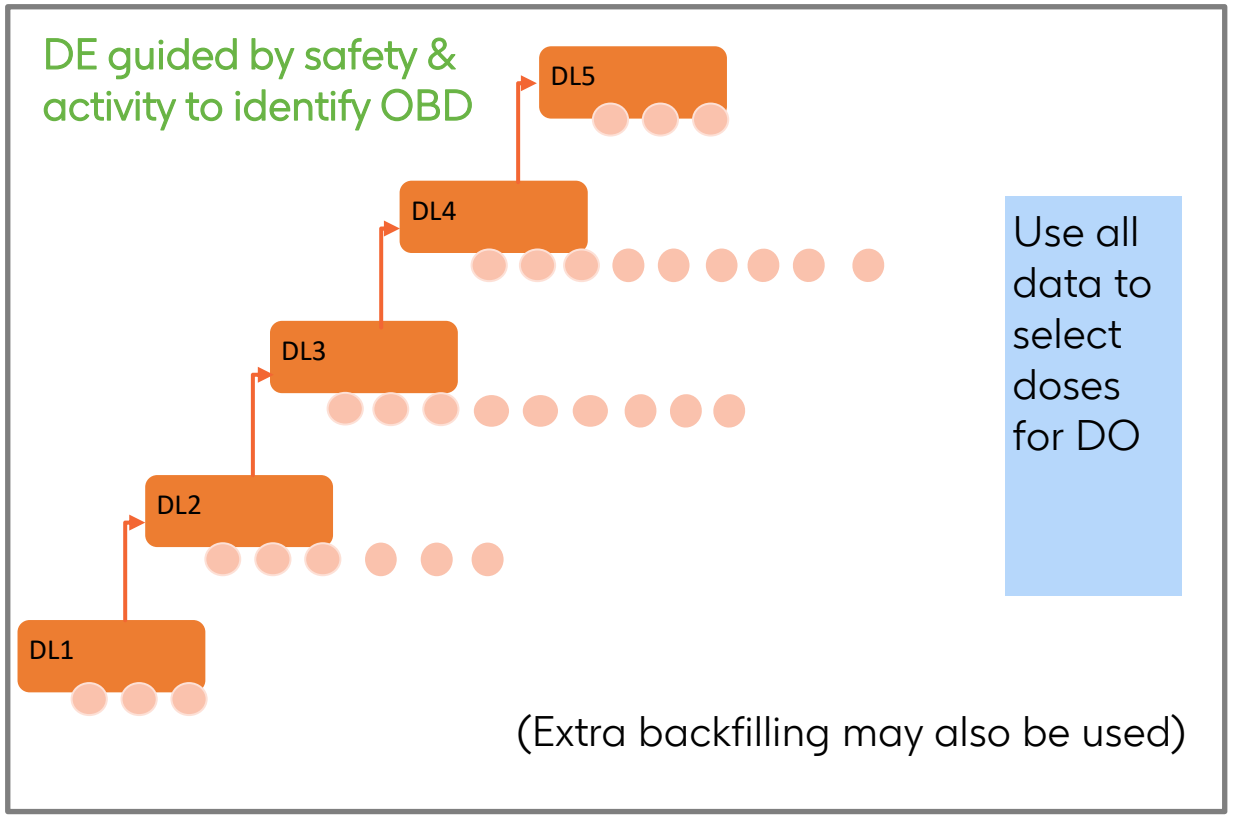
Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Approaches to seamless phase I/II designs

Sequential seamless phase I/IIa design

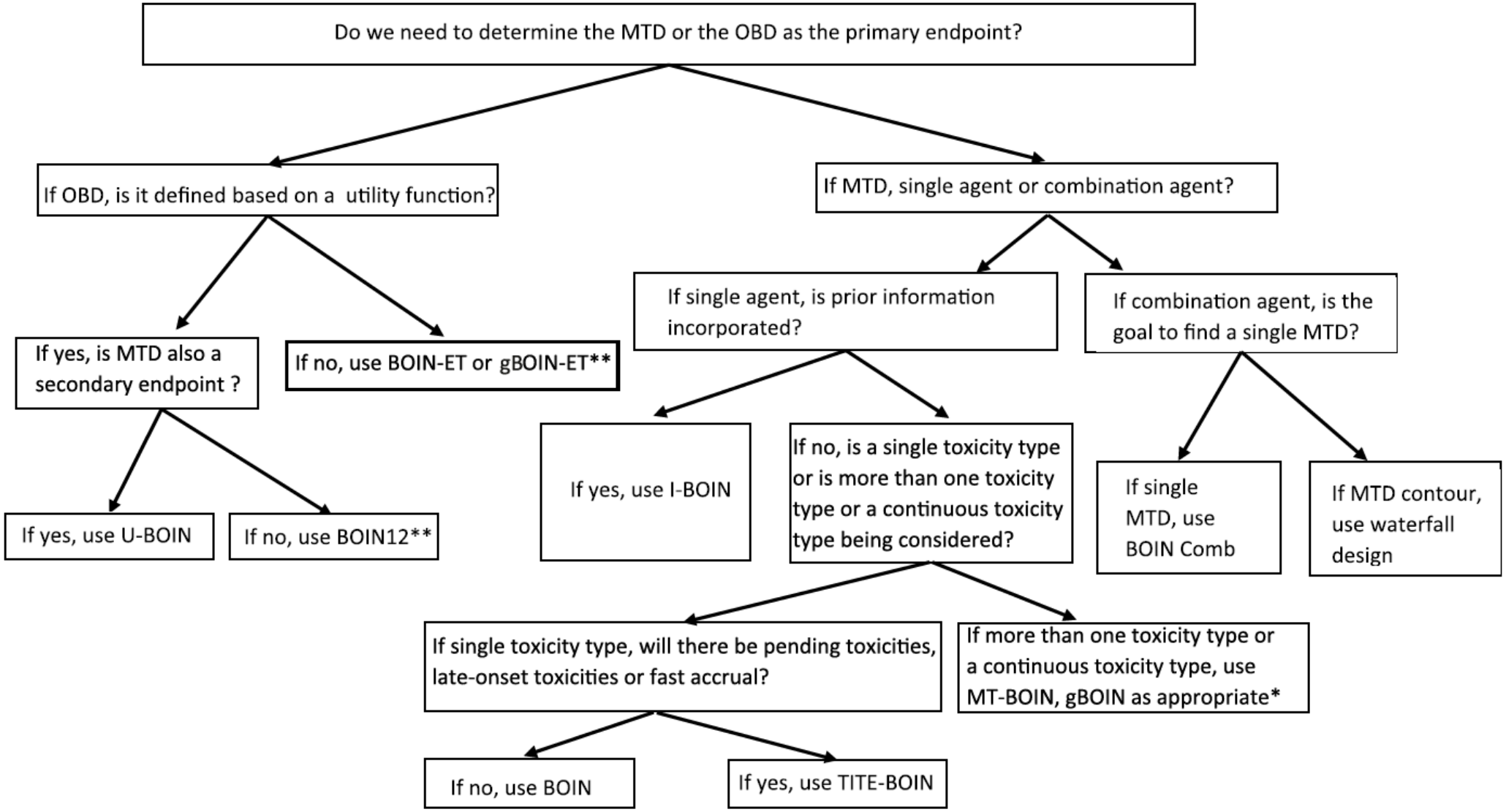


Integrated seamless phase I/IIa design



Grouping of methods	Monotherapy Drugs (Target = OBD)		Combination therapy (Target = OBD)	
	Integrated Method	**Sequential Method**	**Integrated Method**	**Sequential Method**
Delayed efficacy, monotone trend, random allocation, no utility elicitation	Surv-CRM-12 (Andillon *et al.*, 2021)			
Delayed efficacy, non-monotone trend, no Random allocation, utility elicitation			Comb-BOIN12 (Lu *et al.*, 2024)	
Delayed efficacy; non-monotone trend, no random allocation; no utility elicitation	MISO (2023); Isotonic Regression (Qiu *et al.*, 2023)			
Delayed efficacy; non-monotone trend, random allocation; No utility elicitation	SPIRIT (Guo *et al.*, 2018); Generalized phase I - II (Thall, Zang and Yuan, 2023)	Backfill i3+3(Liu *et al.*, 2024)		
Delayed efficacy; non-monotone efficacy trend, Random allocation; utility elicitation	Competing risk outcome (Zhang *et al.*, 2021); BIPSE (Guo and Zang 2021), BOIN-TITE (Zhou *et al.*, 2019)			
No delayed efficacy; monotone trend; no random allocation, no utility elicitation	Bivariate CRM (Braun *et al.*, 2002)			
No delayed efficacy, monotone trend, random allocation, no Utility elicitation	Adaptive Phase I/II (Wages and Conaway, 2014)			
No delayed efficacy, non-monotone trend, no random allocation, no utility elicitation	Combined criteria (Alam *et al.*, 2019); CFO Calibration (Jin and Yin, 2022); Bayesian Eff-Tox Odds ratio (Yin *et al.*, 2006)	STEIN (Lin and Yin, 2017)	A Bayesian dose finding method (Cai and Yuan, 2014)	
No delayed efficacy, non-monotone trend, no random allocation, utility elicitation	BOIN 12-utility based (Lin et al, 2020); EffTox (Thall & Cook, 2004; Thall, Cook and Estley, 2006)		Ordinal toxicity and efficacy method (Houede *et al.*, 2010)	
No delayed efficacy, non-monotone trend, random allocation, utility elicitation	Bayesian adaptive phase I/II in paediatric (Mu *et al.*, 2021)		A Bayesian platform design (Mu *et al.*, 2022; Mu *et al.*, 2024)	
	Monotherapy Drugs (Target =MTD)		**Combination therapy (Target =MTD)**	
	Integrated Method	**Sequential Method**	**Integrated Method**	**Sequential Method**
Delayed efficacy; non-monotone trend; random allocation, no utility elicitation		CR-CRM (Biard *et al.*, 2021)		Bayesian phase I/II with two stages (Jimenez, 202030)
No delayed efficacy; monotone trend; no random allocation, no utility elicitation		Shotgun (Jiang *et al.*, 2021)		
No delayed efficacy; non-monotone trend, no random allocation, no utility elicitation		BOIN-Backfilling (Zhao *et al.*, 2024)		Bayesian method for maximum tolerated dose contour (Zhang and Yuan, 2016)
No delayed efficacy, non-monotone trend, random allocation, no utility elicitation	Adaptive randomisation strategies (Yan *et al.*, 2019)	Bayesian seamless phase I/II design (Pan *et al.*, 2013)	Adaptive phase I/II (Yada and Hamada, 2017)	Combination of cyto-toxic agents (Tighiouart, 2019)

BOIN Suite of Algorithms



Phase 2 Trials

Objective and Learning Outcomes

- **Objective**
  - Introduce Multiple Comparison Procedure – Modelling method
  - Dose-response analysis using MCP-Mod
- **Learning Outcomes**
  - Understand the rationale for MCP-Mod
  - Able to use DoseFinding Package in R
  - Analysis and interpretation of results

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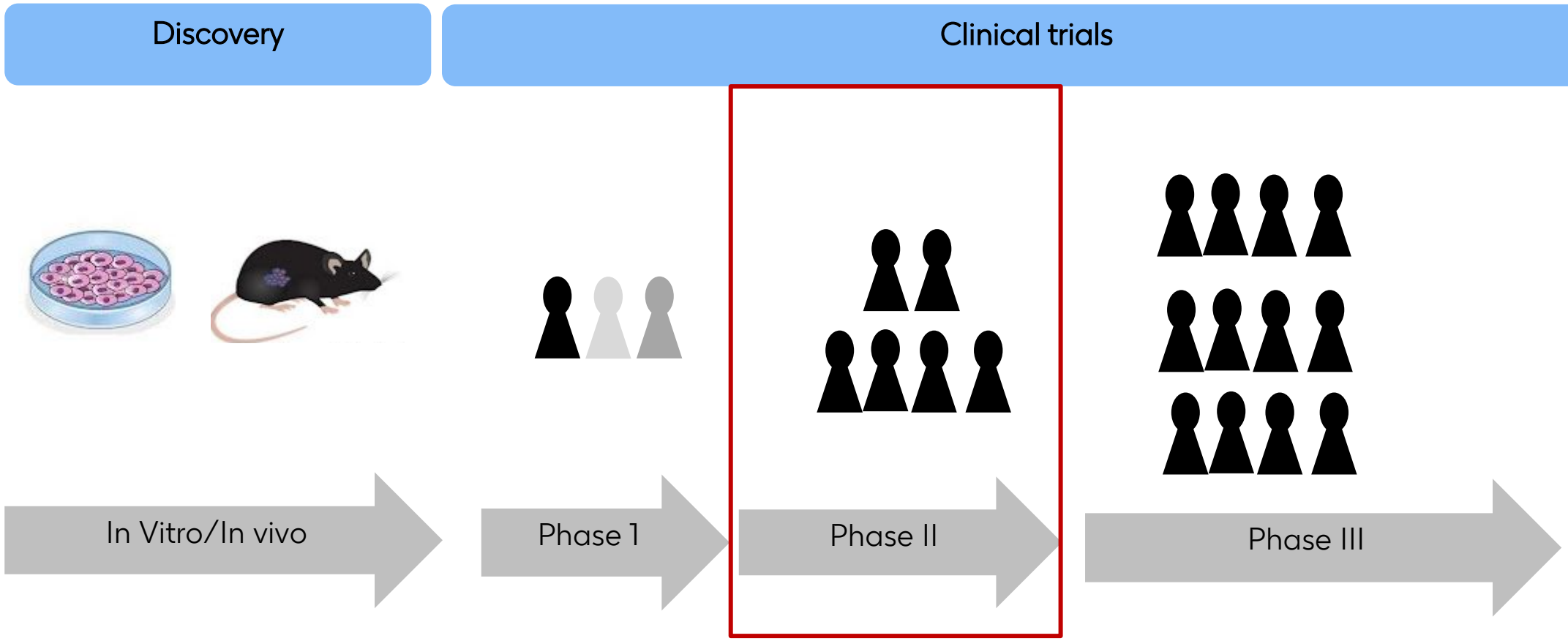
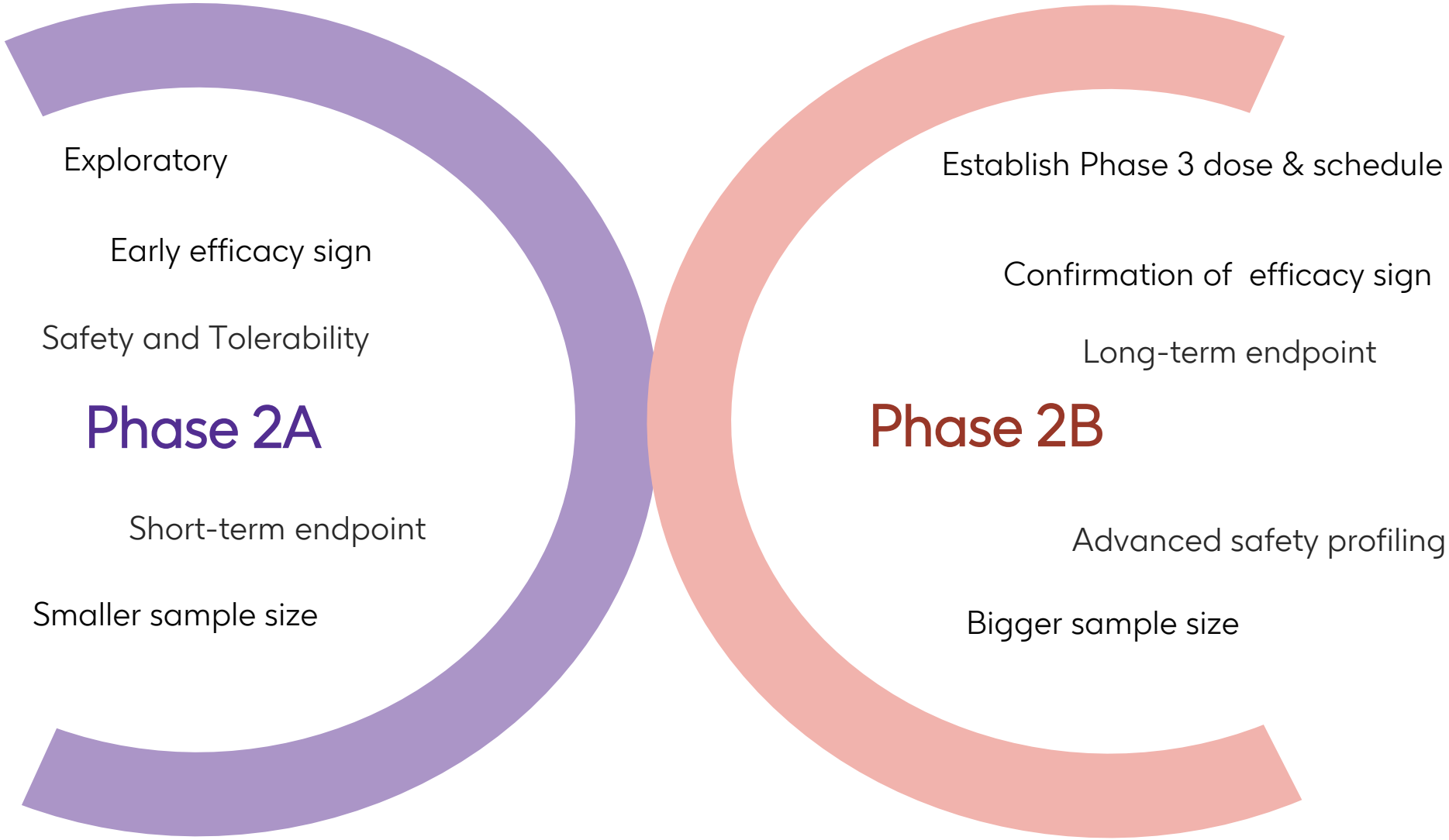
Phase 2 trials



Phase 2 trials

Purpose	Description
Efficacy Assessment	Determine whether the drug exhibits a biological effect in patients. Unlike Phase 1 trials that focus primarily on safety, Phase 2 trials aim to demonstrate the drug's activity against cancer.
Dose Optimization	Identify the dose that provides the best balance between efficacy and toxicity
Safety and Toxicity Profiling	Continue to monitor adverse effects, understanding the safety profile more thoroughly in a larger patient population compared to Phase 1
Biomarker Identification	Identify and validate biomarkers that predict response, resistance, or risk.
Proof of Concept	Provide initial evidence that the drug is effective for a specific cancer type or subtype.

Phase 2A vs Phase 2 B



Common efficacy endpoints in Phase 2

Overall Response Rate (ORR)

➢ The proportion of patients whose cancer shrinks or disappears after treatment.

•**Components:**

- **Complete Response (CR):** Total disappearance of all target lesions.
- **Partial Response (PR):** At least a 30% decrease in the diameter of target lesions.

•**Usage:** ORR serves as a direct measure of a drug's anti-tumor activity and is frequently used as a primary endpoint in Phase 2 trials.

Note: ORR is part of RECISTS outcome categories including Stable Disease (SD) and Progressive Disease (PD)

Common efficacy endpoints in Phase 2

Progression-Free Survival (PFS)

- The duration during which a patient's cancer does not worsen after treatment. It is a time-to-event endpoint

•**Measurement:**

- Time from the start of treatment until disease progression or death.

•**Usage:** It is a more informative endpoint than ORR and it is acceptable as a regulatory endpoint in some cancer types like ovarian cancer.

Other endpoints

- **Overall Survival (OS):** Time from the start of treatment until death from any cause.
- **Time to Progression (TTP):** Time from the start of treatment to the point where cancer growth is first observed.
- **Disease Control Rate (DCR):** The total percentage of patients who achieve a complete response, partial response, or stable disease.
- **Biomarker-focused Endpoints:** Evaluating biomarker changes as indicators of cancer drug effects
- **Quality of Life (QoL):** Evaluating changes in patients' overall well-being, using standardized questionnaires.

PICOS Framework

A good way to gain insights into published clinical trials is using PICOS framework that focuses on the following key features;

P - Population

What is the population of patients included in the clinical trial?

I - Intervention

What is the investigational medicinal product evaluated in the trial?

C - Comparison

What comparator or standard of care used to evaluate clinical benefit?

O - Outcome

What are the endpoints used in the trial and their results?

S – Study design

What is the study design including allocation method and sample size?

Exercise 4

What are the key design features of the Phase II clinical trial of pembrolizumab efficacy and safety in advanced adrenocortical carcinoma – Habra et al. (2019). The paper is available in the course folder

What are the limitation and the strength of the study design?

Exercise 5

What are the key design features of the clinical trial of Dostarlimab or pembrolizumab plus chemotherapy in previously untreated metastatic non-squamous non-small cell lung cancer: the randomized PERLA phase II trial – Lim et al. (2023). The paper is available in the course folder

What are the limitation and the strength of the study design?

Phase II Study Design Methods

Design	Description
Single-Arm Trials	Participants receive the experimental treatment without a control group. This design is often used when the historical outcomes can serve as a comparison, or in cases where ethical considerations prevent withholding treatment.
Randomized Controlled Trials (RCTs):	Participants are randomly assigned to either the experimental or control group, allowing more reliable efficacy and safety comparisons with or without blinding
Adaptive Designs	Allows adaptations like sample size adjustment, dose escalation/de-escalation, and treatment arm additions/removals
Basket Trials	Focuses on patient cohorts across various cancer types sharing a common trait, expanding the scope of investigation
Umbrella Trials	Patients within a single type of cancer are divided into groups, each testing different therapies or combinations.
Platform Trials	Utilizes a master protocol and allows testing of different interventions over time against a common control.

MCP-Mod

Introduction of MCP-Mod

		Null Hypothesis (H_0)	
		True	FALSE
Decision about null hypothesis (H_0)	Don't reject	Correct inference (true negative) (Probability = $1 - \alpha$)	Type II Error (false negative) (Probability = β)
	Reject	Type I Error (false positive) (Probability = α)	Correct inference (true positive) (Probability = $1 - \beta$)

To make correct statistical decision about whether a drug work or not, we need to balance between the Type I Error and Type II Error. Statistical power of a test is 1 – Type II Error.

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Introduction of MCP-Mod

		Null Hypothesis (H_0)	
		True	FALSE
Decision about null hypothesis (H_0)	Don't reject	Correct inference (true negative) (Probability = $1 - \alpha$)	Type II Error (false negative) (Probability = β)
	Reject	Type I Error (false positive) (Probability = α)	Correct inference (true positive) (Probability = $1 - \beta$)

For a single hypothesis tested, there is α chance of a false conclusion, which increases with increase in the number of hypothesis tests. Specifically;

$$FWER = 1 - (1 - \alpha)^K$$

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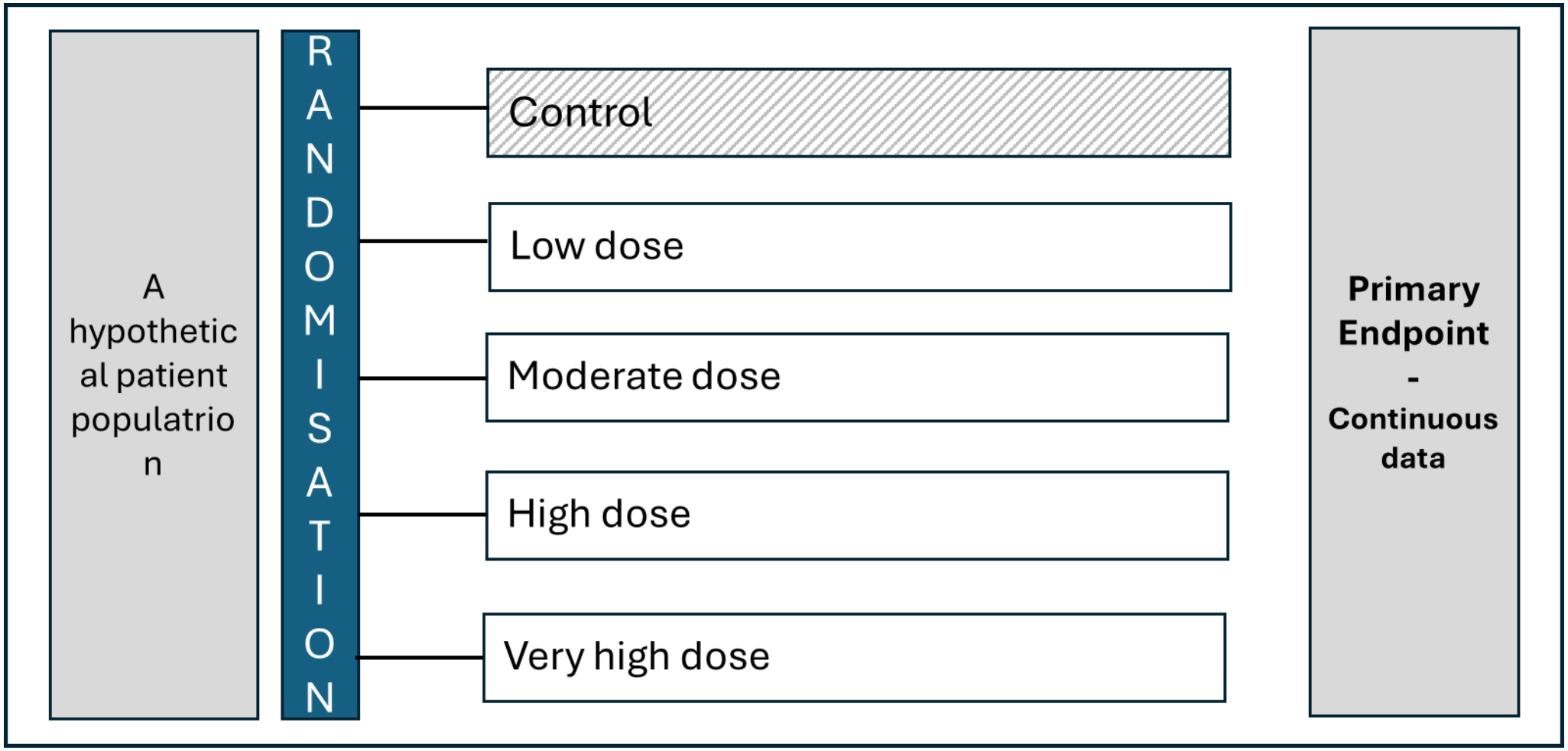
Exercise 5

What is the family wise error rate for testing 3, 5 and 10 hypotheses at alpha level of 5%?

Introduction of MCP-Mod



Assuming all doses are safe, which dose is the most effective dose?

Hypothesis testing

Let $\mu_0, \mu_1, \mu_2, \mu_3$, denote the average response for the control, low, high and very high dose, respectively. Pairwise comparisons between the dose levels will result in large number of hypotheses.

To preserve the FWER, multiplicity correction is required using methods including Tukey test, Bonferroni, Benjamini and Hochberg FDR, etc

Alternatively, each of the active doses can be compared with the control dose and multiplicity correction can be done using the **Dunnett test**

Hypothesis testing

The null hypothesis can be formulated in terms of contrasts between the dose levels.

$$H_0\colon \boldsymbol{c}^T\boldsymbol{\mu} = 0$$

Where $\boldsymbol{c}$ defines the contrast of interests.

$$C = \begin{pmatrix} {c_1}^T \\ \vdots \\ ci^T \\ \vdots \\ cm^T \end{pmatrix} = \begin{pmatrix} c_{10} & \cdots & c_{1k} \\ \vdots & & \vdots \\ c_{i0} & \cdots & c_{ik} \\ \vdots & & \vdots \\ c_{m0} & \cdots & c_{mk} \end{pmatrix}$$

- m denotes the number of pairwise comparison

  i.e $\binom{k}{2} = \binom{5}{2} = 10$ for our hypothetical trial
- k is the number of doses i.e $k = 5$ for our hypothetical trial

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Hypothesis testing

The null hypothesis can be formulated in terms of contrasts between the dose levels.

$$H_0\colon \boldsymbol{c}^T\boldsymbol{\mu} = 0$$

For Dunnett Test

$$C = \begin{pmatrix} -1 & 1 & 0 & 0 & 0 \\ -1 & 0 & 1 & 0 & 0 \\ -1 & 0 & 0 & 1 & 0 \\ -1 & 0 & 0 & 0 & 1 \end{pmatrix}$$

- Number of tests reduces to 4 instead of 10 hypotheses.

The maximum test statistic is compared against $t^4_{1-\alpha,v,\boldsymbol{R}}$. $\boldsymbol{R}$ is correlation matrix and v is the degree of freedom i.e $\sum n_i - k$

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Introduction of MCP-Mod

Traditionally, dose-finding studies often employed pairwise comparisons between doses and placebo or linear models to identify dose-response relationships. These methods are straightforward but can be inefficient and sometimes misleading when dealing with complex dose-response relationships.

As pharmaceutical development processes evolved, there was a clear need for methodologies that could intelligently and robustly model dose-response curves, handle multiple possible models, and incorporate statistical testing to ensure scientifically backed decisions.

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Introduction to MCP-Mod

Let $d_1, \dots, d_k$ denotes the K doses in a trial with $d_1 = 0$ representing the control dose or standard of care. The responses of patients in the trial can be expressed as

$$Y_{ij} = f(d_i, \boldsymbol{\theta}) + \epsilon_{ij}$$

$$\epsilon_{ij} \sim N(0, \sigma^2)$$

- $i = 1, \dots, k$ and $j = 1, \dots, n_i$. n_i denotes the number of patients allocated to dose d_i
- ϵ_{ij} is independent with σ^2 an unknown residual variance parameter.
- The function f depends on dose and unknown $\boldsymbol{\theta}$
- The mean dose response at each dose level is denoted by $\mu' = (\mu_1, \dots, \mu_k)$
- The sample means are denoted by $\bar{Y}' = (\bar{y}_1, \dots, \bar{y}_k)$

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Candidate models

Model	$\boldsymbol{f(d,\theta)}$
Emax	$E_0 + E_{max}\frac{d}{ED_{50}+d}$
Sigmoid Emax	$E_0 + E_{max}\frac{d^h}{{ED_{50}}^h+d^h}$
Logistic	$E_0 + E_{max}/\{1+exp[(ED_{50}-d)/\delta]\}$
Exponential	$E_0 + E_1(exp\left(\frac{d}{\varphi}\right)-1)$
Linear	$E_0 + E_1 d$
Linear in log	$E_0 + E_1\log(d+off)$

- E_0- Placebo or control effect
- E_{max} - Maximum effect
- ED_{50} - dose at half of asymptotic maximum effect
- h- hill parameter
- E_1- slope parameter
- δ – steepness parameter
- φ- convex parameter
- off – an offset to add to dose, particularly when it has zero value

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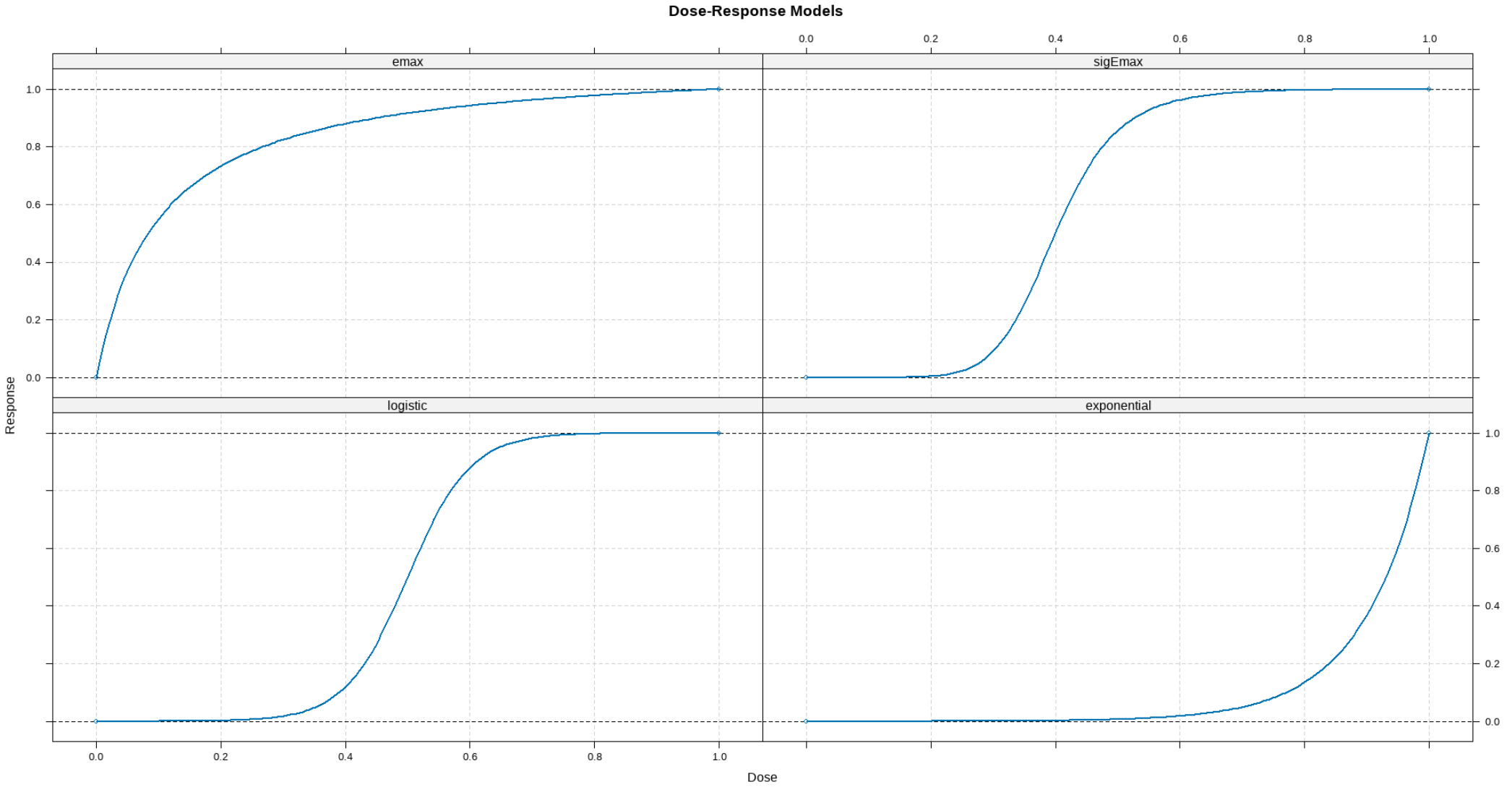
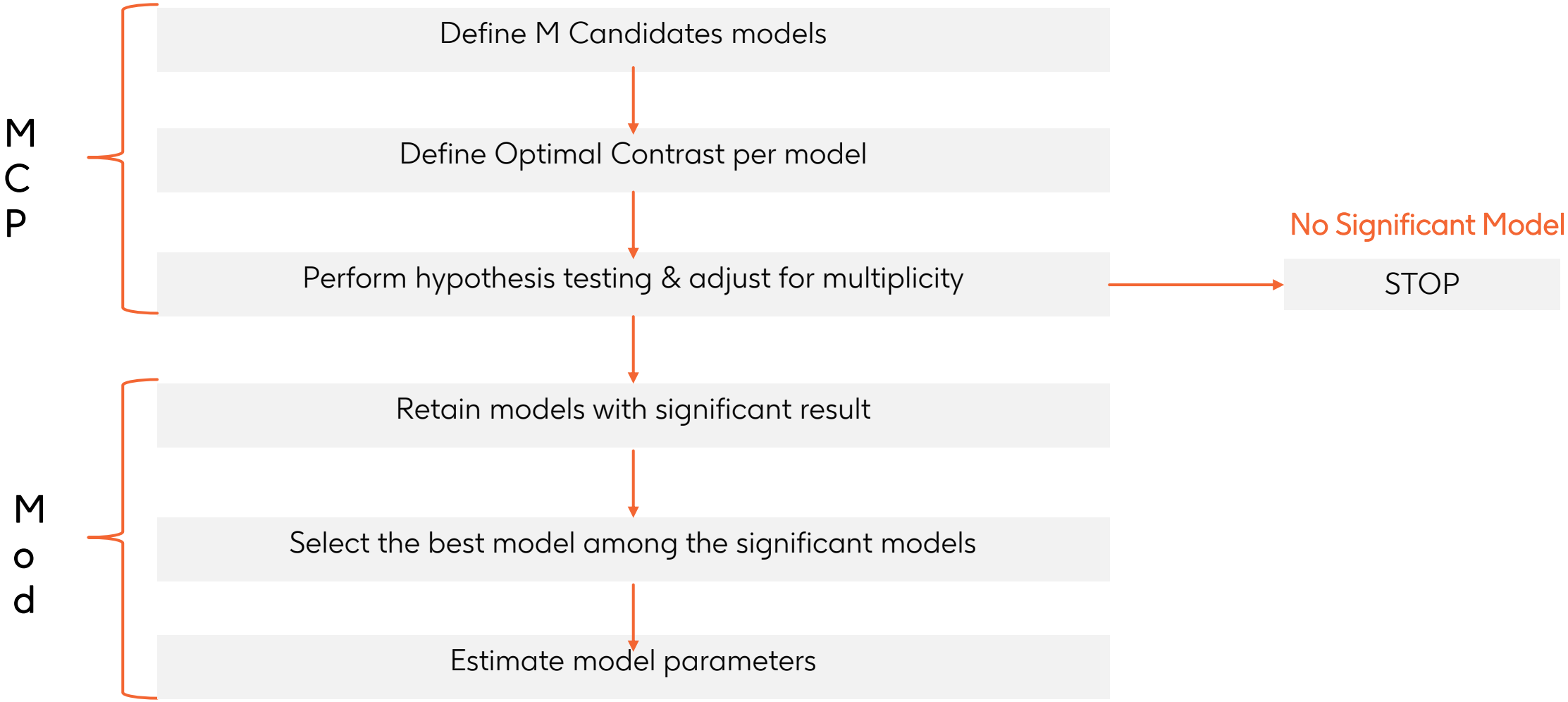
Candidate Models



MCP-Mod steps



Dose response analysis: Continuous Endpoint

(Examples are based on non-oncology studies)

Introduction to MCP-Mod

Let $d_1, \dots, d_k$ denotes the K doses in a trial with $d_1 = 0$ representing the control dose or standard of care. The responses of patients in the trial can be expressed as

$$Y_{ij} = f(d_i, \boldsymbol{\theta}) + \epsilon_{ij}$$

$$\epsilon_{ij} \sim N(0, \sigma^2)$$

- $i = 1, \dots, k$ and $j = 1, \dots, n_i$. n_i denotes the number of patients allocated to dose d_i
- ϵ_{ij} is independent with σ^2 an unknown residual variance parameter.
- The function f depends on dose and unknown $\boldsymbol{\theta}$
- The mean dose response at each dose level is denoted by $\mu' = (\mu_1, \dots, \mu_k)$
- The sample means are denoted by $\bar{Y}' = (\bar{y}_1, \dots, \bar{y}_k)$

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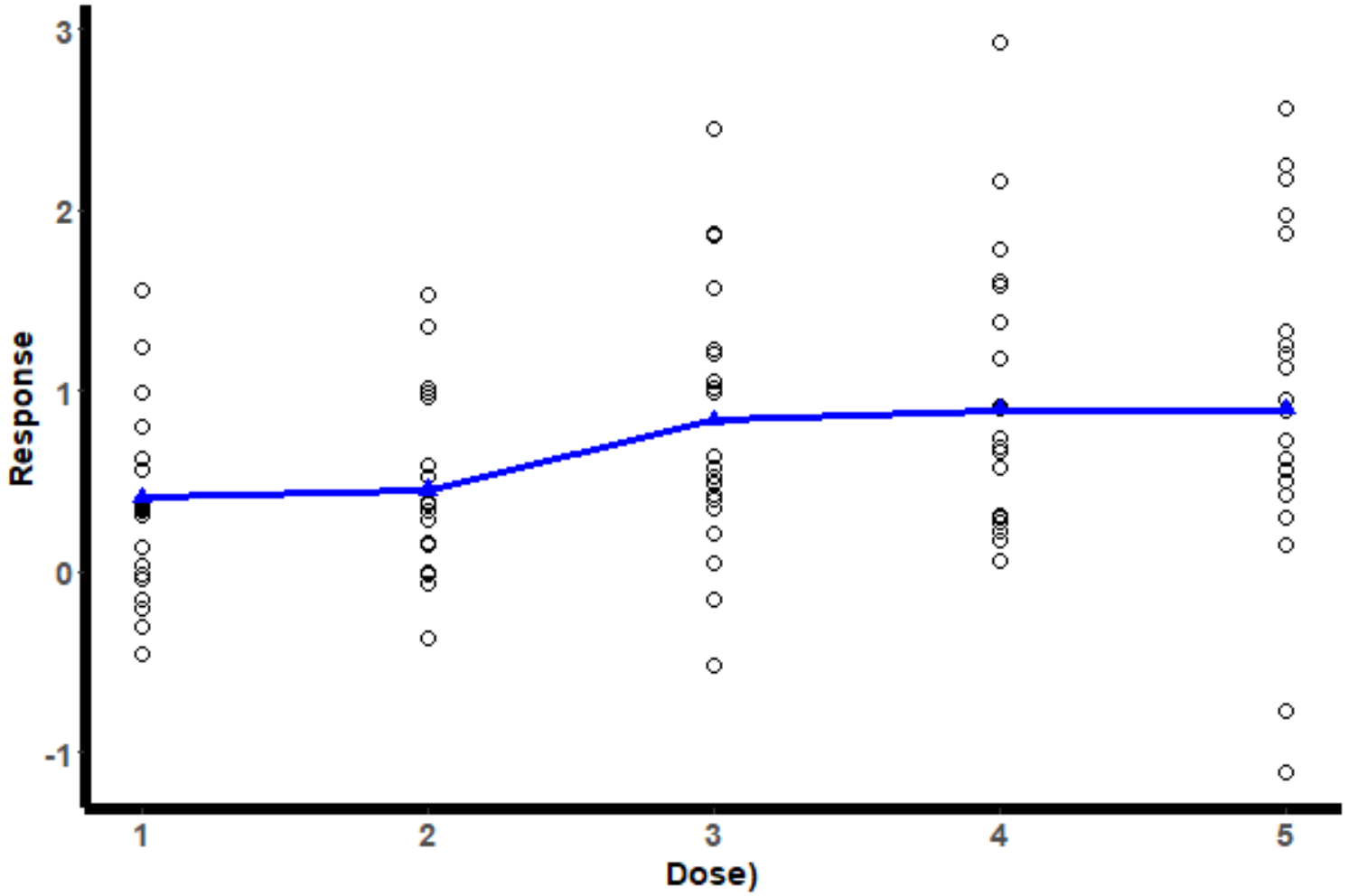
Data – simulated data

Safety and efficacy data on Glycopyrronium Bromide (NVA237) in patients with stable Chronic Obstructive Pulmonary Disease (COPD). The primary endpoint in this study was the mean of two measurements of forced expiratory volume in 1 second (FEV1) at 23h 15min and 23h 45min post dosing, following 7 days of treatment. The doses of interest are placebo group and the four dose groups (12.5, 25, 50, and 100µg).

Data



Candidate models

What are the likely candidate models?

Hypothesis testing

Assuming four candidate models, emax1, emax2, sigEmax and quadratic. The null hypothesis for equal average response across doses can be formulated as

$$H_0: \boldsymbol{c}^T \overline{\boldsymbol{Y}} = 0$$

The contrast matrix is defined per model and can be obtained using the following

```
# define doses and models
doses <- c(0, 12.5, 25, 50, 100)
mods <- Mods(emax = c(2.6, 12.5), sigEmax =
c(30.5, 3.5), quadratic = -0.00776, placEff =
1.25, maxEff = 0.15, doses = doses)

optC <- optContr(mods, w=1)
print(optC)
```

Doses	emax1	emax2	sigEmax	quadratic
0	-0.886	-0.813	-0.486	-0.723
12.5	0.116	-0.101	-0.439	-0.240
25	0.211	0.136	-0.120	0.140
50	0.265	0.326	0.448	0.587
100	0.294	0.452	0.597	0.236

Contrast for each model must sum to zero

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Hypothesis testing

MCTtest function in DoseFinding package performs the multiple comparison procedure

```
fitlm <- lm(FEV1 ~ factor(dose) -
       1, data = NVA)

mu_hat <- coef(fitlm)

S_hat <- vcov(fitlm)

anova_df <- fitlm$df.residual

test_general <- MCTtest(dose = doses,
       resp = mu_hat, S = S_hat, df =
       anova_df, models = mods, type
       = "general")
```

```
Multiple Contrast Test

Contrasts:
      emax1  emax2 sigEmax quadratic
0    -0.886 -0.813  -0.486    -0.723
12.5  0.116 -0.101  -0.439    -0.240
25    0.211  0.136  -0.120     0.140
50    0.265  0.326   0.448     0.587
100   0.294  0.452   0.597     0.236

Contrast Correlation:
          emax1 emax2 sigEmax quadratic
emax1     1.000 0.957   0.648     0.867
emax2     0.957 1.000   0.839     0.929
sigEmax   0.648 0.839   1.000     0.844
quadratic 0.867 0.929   0.844     1.000

Multiple Contrast Test:
          t-Stat  adj-p
emax2      7.443 <0.001
quadratic  7.016 <0.001
emax1      6.937 <0.001
sigEmax    6.676 <0.001
```

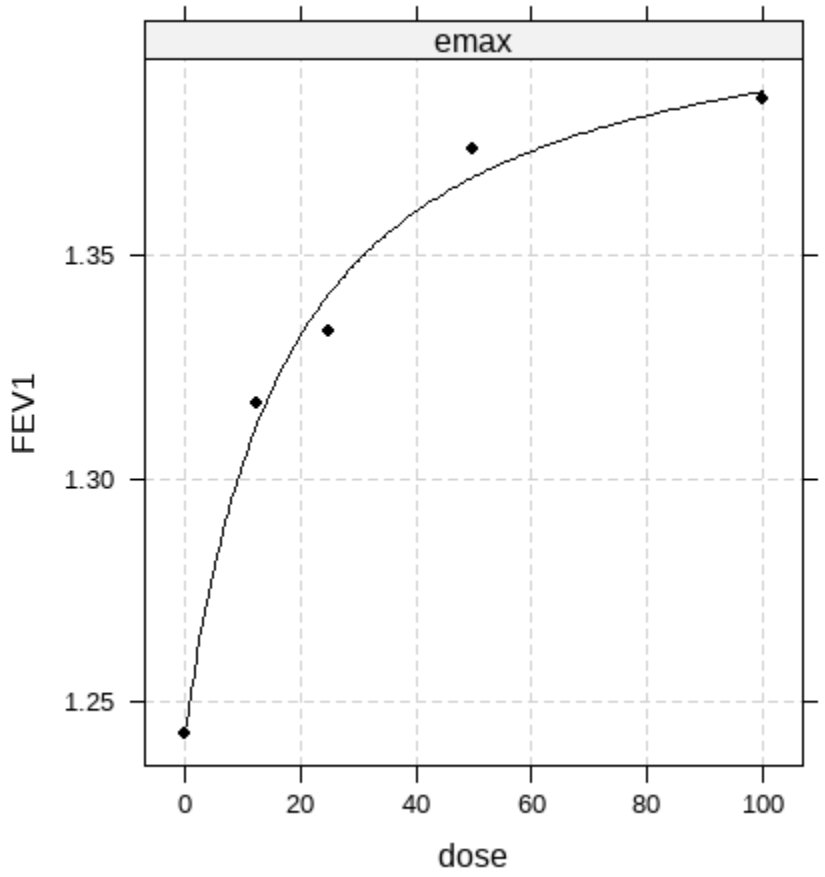
- All the candidate models resulted in significant results, but which model to selected for estimating MED?

Non-linear models

Fit **Emax** model to the data.

```
fit_single <- fitMod(dose, FEV1, NVA,
                     model    = "emax")

plot(fit_single)
```




```
Model: emax
Fit-type: normal

Coefficients dose-response model
     e0    eMax    ed50
 1.2430  0.1693 18.1500

Degrees of freedom: 297
Residual standard error: 0.1159
```

Non-linear models

Fit **Sigmoid Emax** model to the data.

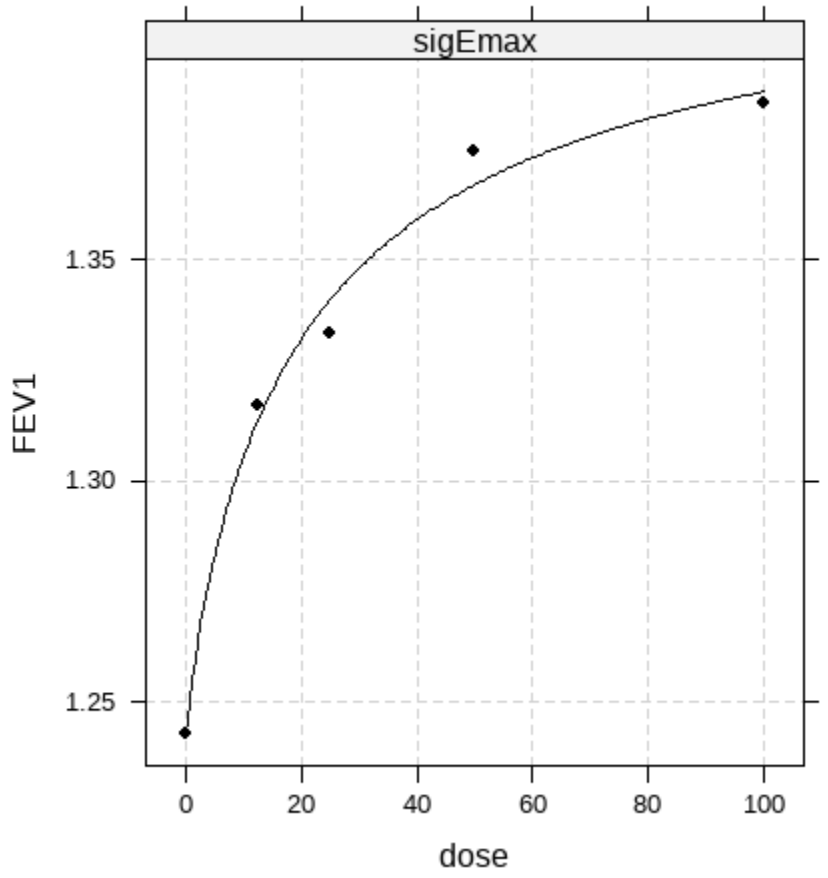
```
fit_single <- fitMod(dose, FEV1, NVA,
                     model    = "sigEmax")

plot(fit_single)
```

```
Model: sigEmax
Fit-type: normal

Coefficients dose-response model
     e0    eMax    ed50       h
 1.2430  0.1815 20.9900  0.8704

Degrees of freedom: 296
Residual standard error: 0.1161
```



Non-linear models

Fit **Quadratic** model to the data.

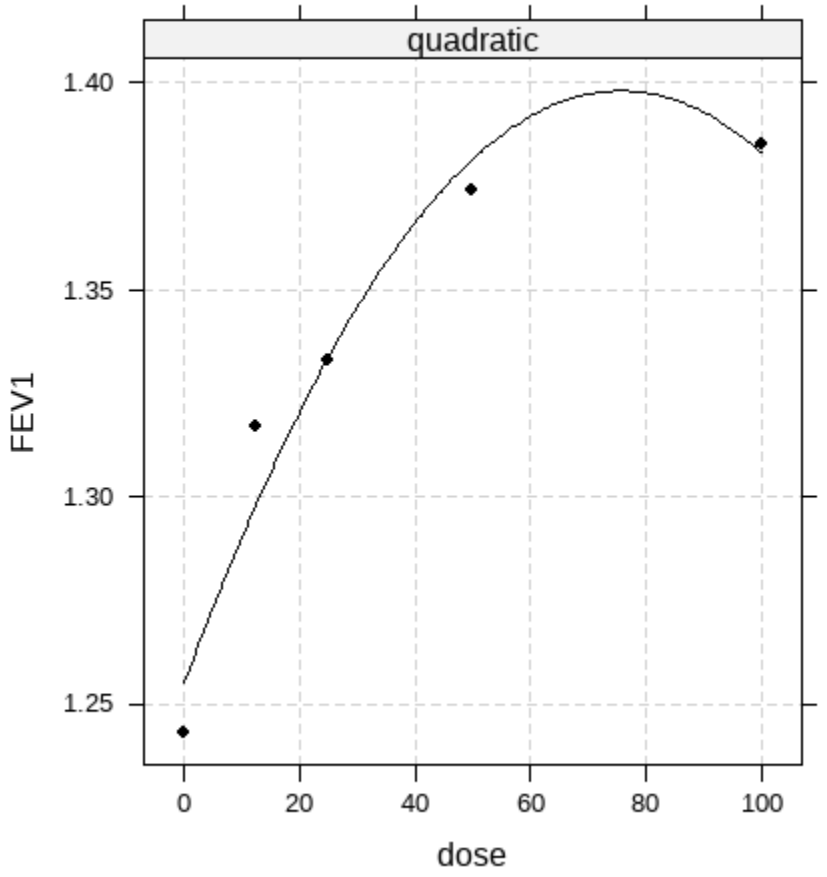
```
fit_single <- fitMod(dose, FEV1, NVA,
                     model    = “quadratic")

plot(fit_single)
```

```
Model: quadratic
Fit-type: normal

Coefficients dose-response model
        e0          b1          b2
 1.255e+00   3.780e-03 -2.496e-05

Degrees of freedom: 297
Residual standard error: 0.1163
```



Model selection

The best model can be selected using

- The model with the largest t-statistics
- Akaike Information Criterion – AIC.
  Smaller value is better

$$= -2ln(\hat{L}) + 2$$

- Bayesian Information Criterion – BIC.
  Smaller value is better

$$= -2ln(\hat{L}) + pln(n)$$

p = number of parameters

n = number of data points

Model	AIC Value
Emax	-436.5819
Sigmoid Emax	-434.6034
Quadratic	-434.7099

Which model is the best model?

Group Work 2

Analyse the dose response data “DoseRespDataCont.csv” to determine if there is a dose-response relationship between PD marker (Response) and dose , and if there is, what dose is necessary to achieve 50% response using the PD marker?

Dose response analysis: Binary Endpoint

(Examples include a non-oncology study)

Data

Assume a dose-finding study is planned for a hypothetical investigational treatment in atopic dermatitis, for the binary endpoint Investigator's Global Assessment (IGA). The treatment is tested with doses 0, 0.5, 1.5, 2.5, 4. It is assumed the response rate for placebo will be around 10%, while the response rate for the top dose may be 35%. This is an example where the generalized MCP-Mod approach can be applied, i.e. dose-response testing and estimation will be performed on the logit scale.

Dose (μg)	y	n
0	14	100
0.5	24	100
1.5	26	100
2.5	33	100

This lesson uses simulated data

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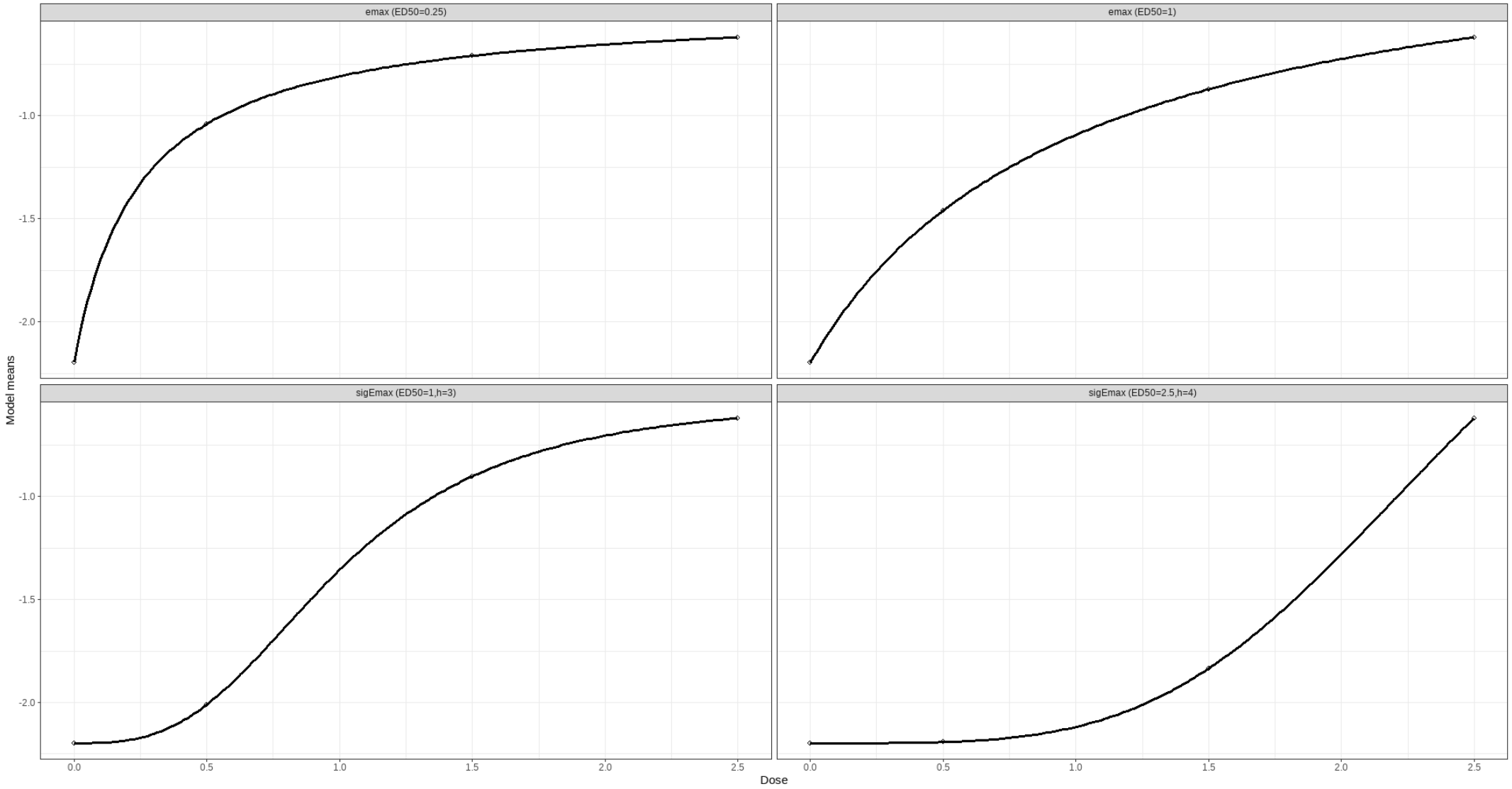
Candidate models



Hypothesis Testing

The binary response can be analysed using a generalized linear model with binomial distribution and a logit link

$$Y_k \sim Binomial(p_k, n_k)$$

$$logit(p_k) \sim \beta_k$$

$$H_0: \boldsymbol{c}^T \overline{\boldsymbol{\beta}} = 0$$

```
# define doses and models

logit <- function(p) log(p / (1 - p))inv_logit <-
function(y) 1 / (1 + exp(-y))

doses <- c(0, 0.5, 1.5, 2.5)

mods <- Mods(emax = c(0.25, 1), sigEmax =
        rbind(c(1, 3), c(2.5, 4)), placEff =
        logit(0.1), maxEff = logit(0.35)-
        logit(0.1),doses = doses)

optC <- optContr(mods, w=1)

print(optC)
```

Dose	emax1	emax2	sigEmax1	sigEmax2
0	-0.839	-0.749	-0.561	-0.376
0.5	0.081	-0.143	-0.424	-0.372
1.5	0.343	0.342	0.389	-0.096
2.5	0.415	0.550	0.596	0.843

Contrast for each model must sum to zero

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Hypothesis testing

```
fit_nocov <- glm(Response~factor(Dose) + 0, data =
            binData, family = binomial)

mu_hat <- coef(fit_nocov)

S_hat <- vcov(fit_nocov)

MCTtest(doses, mu_hat, S = S_hat, models = mods,
type = "general")
```

```
Multiple Contrast Test

Contrasts:
     emax1  emax2 sigEmax1 sigEmax2
0   -0.802 -0.653   -0.444   -0.274
0.5 -0.025 -0.282   -0.530   -0.412
1.5  0.333  0.298    0.332   -0.167
2.5  0.495  0.637    0.642    0.853

Contrast Correlation:
         emax1 emax2 sigEmax1 sigEmax2
emax1    1.000 0.953    0.802    0.591
emax2    0.953 1.000    0.942    0.772
sigEmax1 0.802 0.942    1.000    0.831
sigEmax2 0.591 0.772    0.831    1.000

Multiple Contrast Test:
         t-Stat   adj-p
emax2     2.984 0.00348
emax1     2.968 0.00383
sigEmax1  2.595 0.01092
sigEmax2  2.431 0.01704
```

- All the candidate models resulted in significant results, but which model is the best model?

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Non-linear models

Fit **Emax** model to the data.

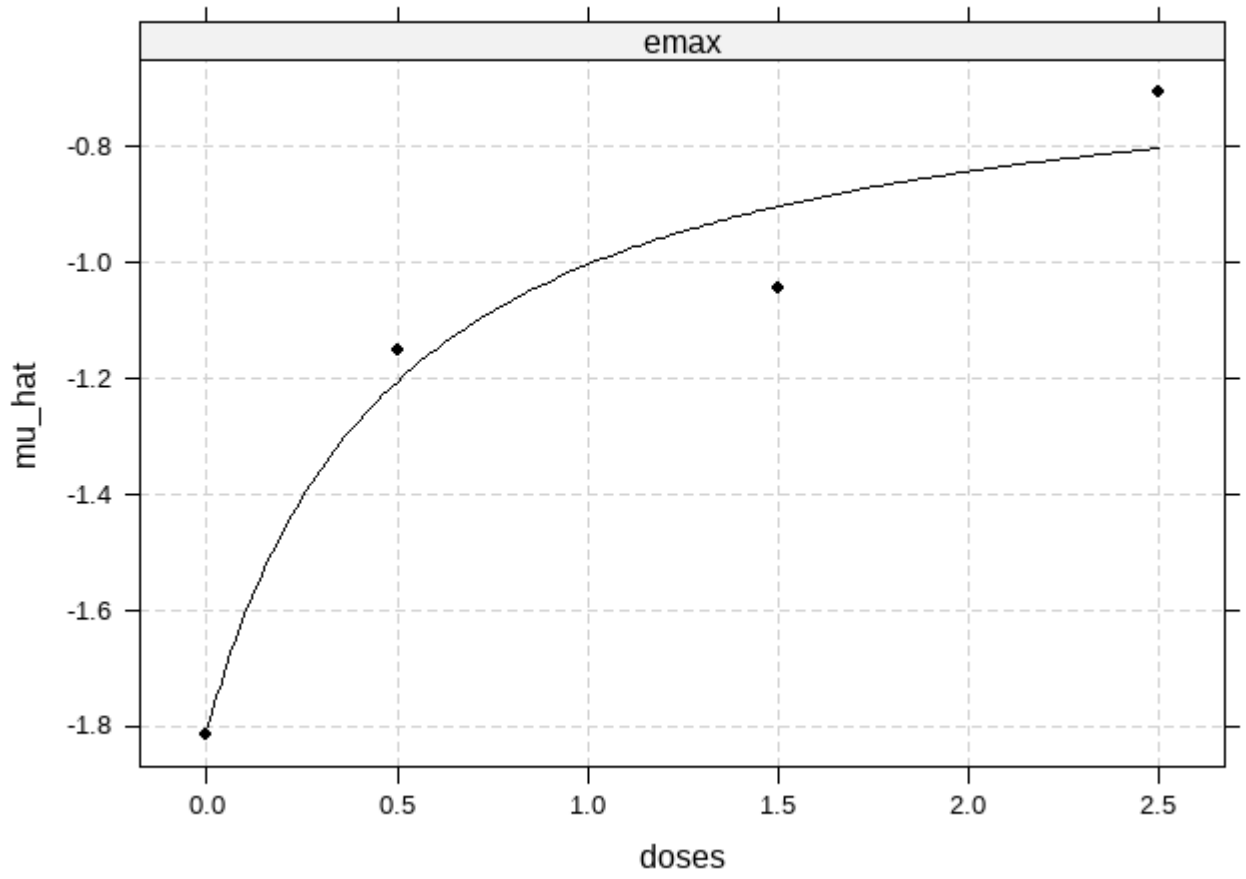
```
fit_Emax <- fitMod(doses, mu_hat, S =
                   S_hat, model = "emax")

plot(fit_Emax)
```

```
Model: emax
Fit-type: normal

Coefficients dose-response model
      e0    eMax    ed50
-1.8080  1.2060  0.5007

Degrees of freedom: 1
Residual standard error: 0.1791
```



Non-linear models

Fit **Sigmoid Emax** model to the data.

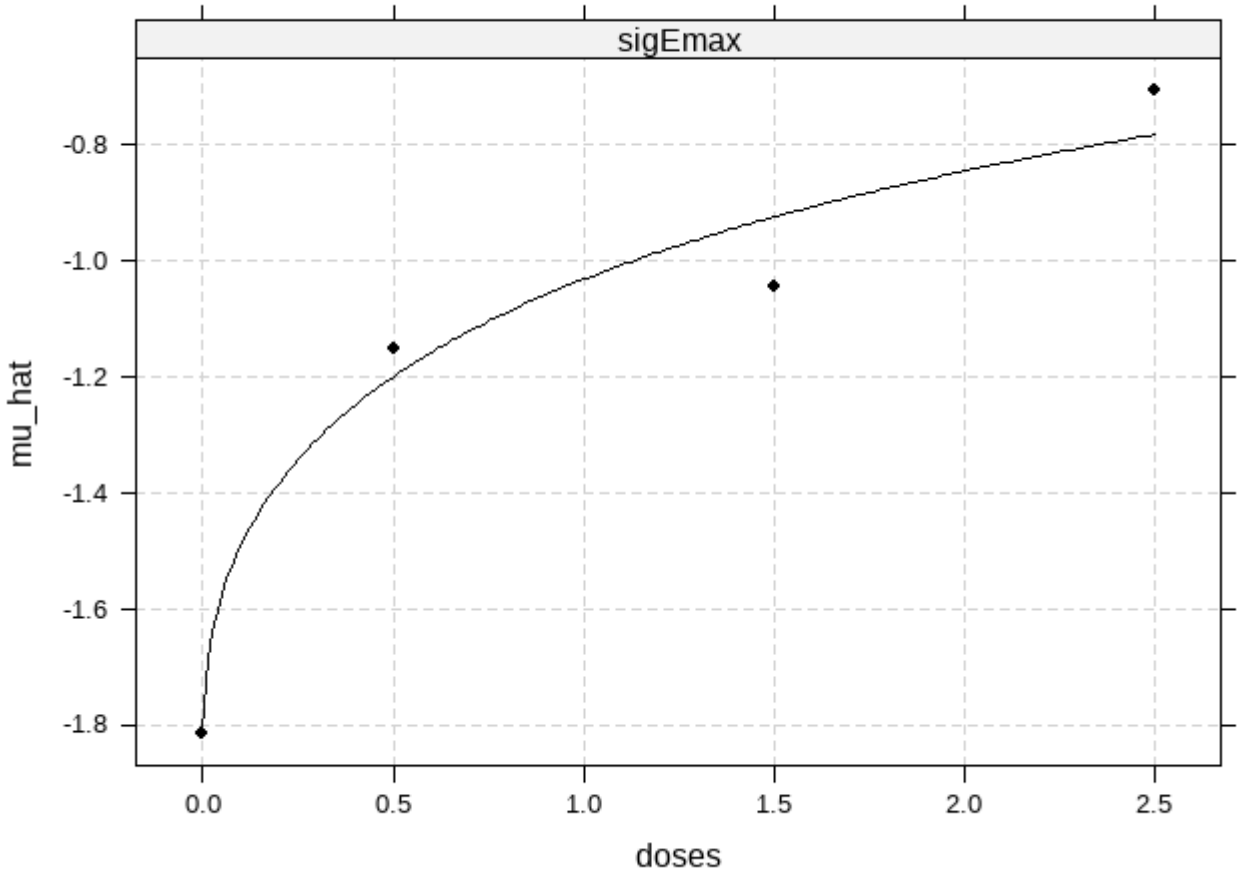
```
fit_sigEmax <- fitMod(doses, mu_hat, S
=              S_hat, model = "emax")

plot(fit_sigEmax)
```

```
Model: sigEmax
Fit-type: normal

Coefficients dose-response model
     e0    eMax    ed50       h
-1.813   2.289   3.750   0.500

Degrees of freedom: 0
Residual standard error: Inf
```



Model selection

The best model can be selected using

- The model with the largest t-statistics
- Akaike Information Criterion – AIC.
  Smaller value is better

$$= -2ln(\hat{L}) + 2$$

- Bayesian Information Criterion – BIC.
  Smaller value is better

$$= -2ln(\hat{L}) + pln(n)$$

p = number of parameters

n = number of data points

Model	AIC Values
Emax	0.048
Sigmoid Emax	0.617

Which model is the best model?

Group Work 3

Analyse the dose response data “DoseRespDataBin.csv” to determine if there is a dose-response relationship between PD marker (Response) and dose , and if there is, what dose is necessary to achieve 50% response using the PD marker?

SYMSTAT 2025

Dose response analysis using Bayesian variable selection method

Adetayo Kasim

Outline

- Introduction
- Bayesian Approach
- Case Study
- Questions

Introduction

Dose-response studies within OMICs have similar features as the traditional dose response studies. However;

- Thousands of genes/protein/peptides are measured under increasing dose of a compound.
- No known function relationship between response and dose
- Number of dose is usually small.

The main objective is to evaluate if the expression of a gene is dose-dependent

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Case Study

HESCA : Human epidermal squamous carcinoma cell lines

	EGF (ng/ml)			
Dose	0	1	10	100
# of arrays	3	3	3	3

- 4 dose levels.
- 12 arrays.
- 16,998 genes measured per array

- A dose-response microarray oncology experiment designed to better understand the biological effects of growth factors in human tumor.

(Bijnens *et al.*, 2012)

Method can be applied to any omics platform with appropriate adjustment

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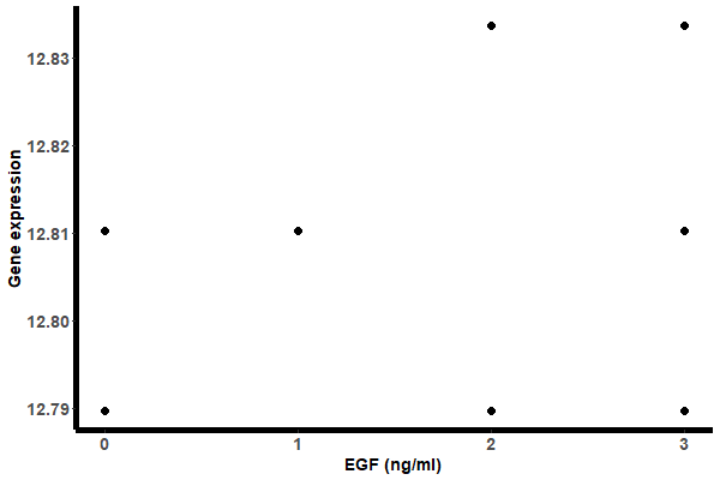
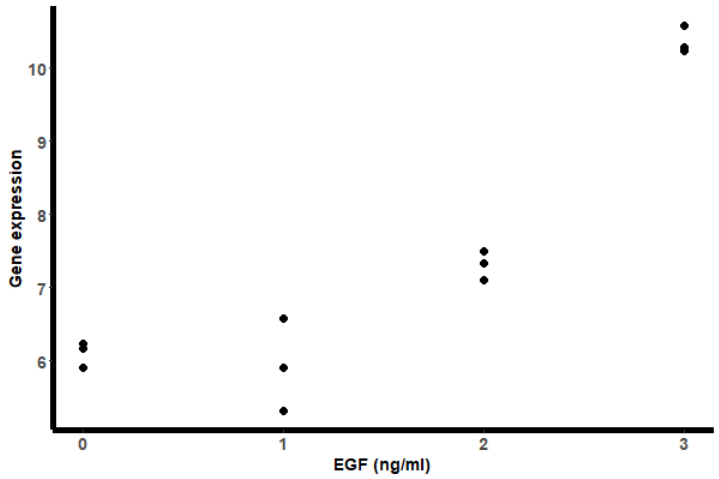
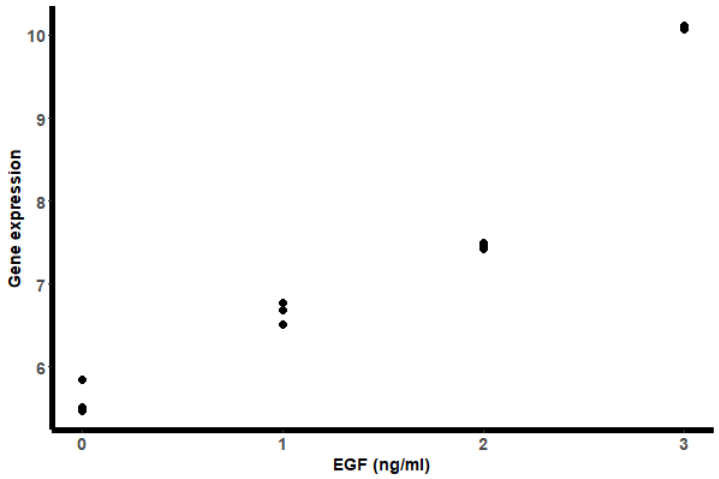
Case Study



Gene 4910



Gene 3350



Gene 3680

These three genes are selected for illustration only

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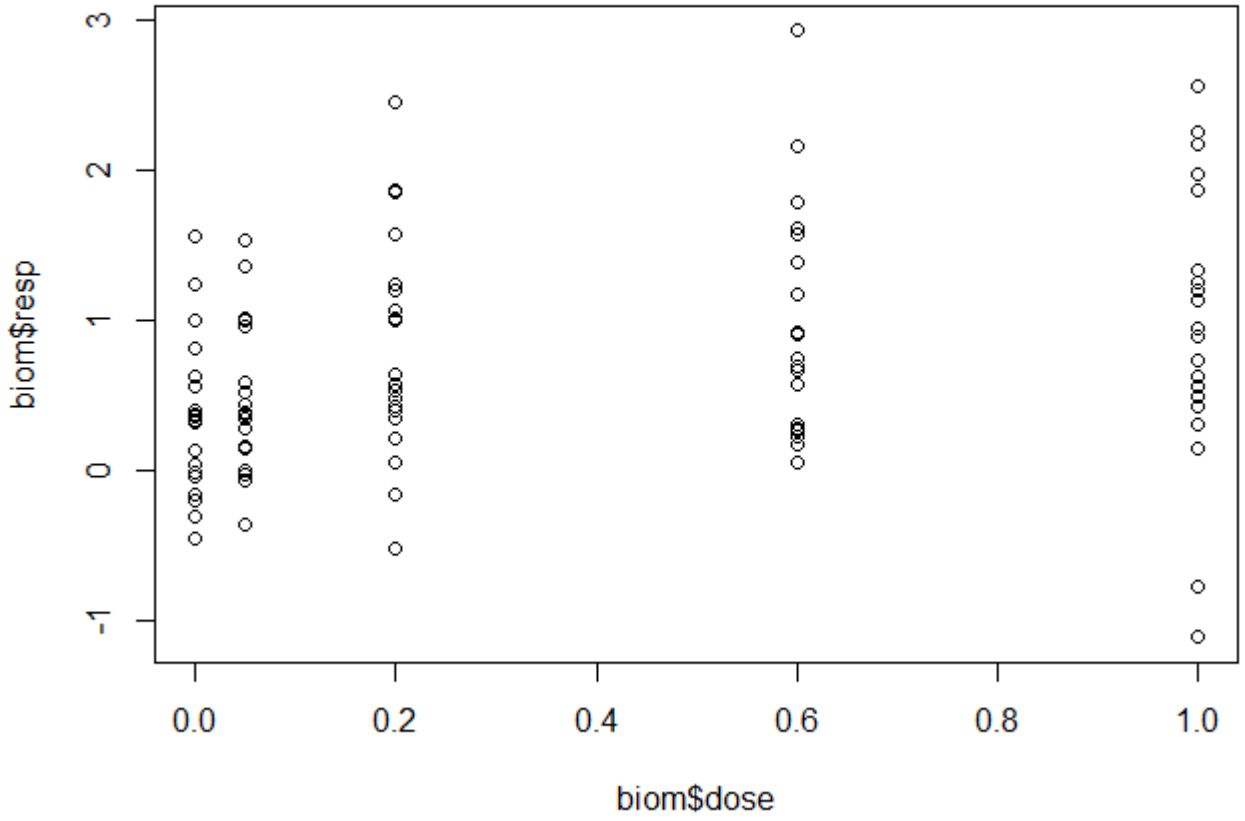
Case Study

Randomised controlled trial containing four active dose group and a place group



Dose	0	0.05	0.20	0.60	1
# of arrays	20	20	20	20	20

- PoC decision criteria

$$P(g_o|Data) < 0.05$$

Method

Let $d_1, \ldots, d_k$ denotes the K doses in a trial with $d_1 = 0$ representing the control dose or standard of care. The responses of patients in the trial can be expressed as

$$Y_{ij} = f(d_i, \boldsymbol{\theta}) + \epsilon_{ij}$$

$$\epsilon_{ij} \sim N(0, \sigma^2)$$

- $i = 1, \ldots, k$ and $j = 1, \ldots, n_i$. n_i denotes the number of patients allocated to dose d_i
- ϵ_{ij} is independent with σ^2 an unknown residual variance parameter.
- The function f depends on dose and unknown $\boldsymbol{\theta}$
- The mean dose response at each dose level is denoted by $\mu' = (\mu_1, \ldots, \mu_k)$
- The sample means are denoted by $\bar{Y}' = (\bar{y}_1, \ldots, \bar{y}_k)$

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Methods

- Pairwise comparisons
  - No assumption required about the nature of the dose-response relationship
  - Inference restricted to the set of dose under investigation and multiplicity correction is required
- Model-based approach
  - Assumes a functional relationship between response and dose
  - Requires set of candidate parametric models, mostly non-linear models
- Model selection
  - To determine the best model for estimating minimum effective dose.

(Bretz et al. 2005, Lin *et al.* 2012)

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Frequentist approach

Assuming unknown functional form, dose-response data can be analysed using One-way ANOVA under simple order restrictions.

$$Y_{ij} = N(\mu_i, \sigma^2)$$

Where dosed-specific means (μ_i) are constrained to be monotone

$$\mu_0 \leq \mu_1 \leq \cdots \leq \mu_K$$

$i = 0, \ldots, K-1$ denotes dose and $j = 1, \ldots, n_i$ denotes observation per dose. K is the number of dose.

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Frequentist approach

Establishing dose-response signal reduces to testing two hypothesis

$$H_0: \mu_0 = \mu_1 = \mu_2 = \ldots = \mu_K$$

versus

$$H_a: \mu_0 \leq \mu_1 \leq \mu_2 \leq \ldots \leq \mu_K$$

With at least one strict inequality.

Frequentist approach

- Isotonic Regression
  - The average response per dose constrained to be monotone using Pool Adjacent Violator Algorithm (PAVA, Robertson *et al.*, 1988)
- Likelihood Ratio Test (Barlow, 1972)
  - Compare unconstrained and order restricted trends based on isotonic means
- Multiple Contrast Test (MCT: Murkerjee et al., 1987)
  - Compare active dose and control dose using contrast tests (Williams 1971, 1972; Marcus 1976)

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Frequentist approach

Model selection approach to simultaneously establish dose-response relationship and to determine the minimum effect dose (MED)

$$H_0\colon \mu_0 = \mu_1 = \mu_2 = \ldots = \mu_K$$

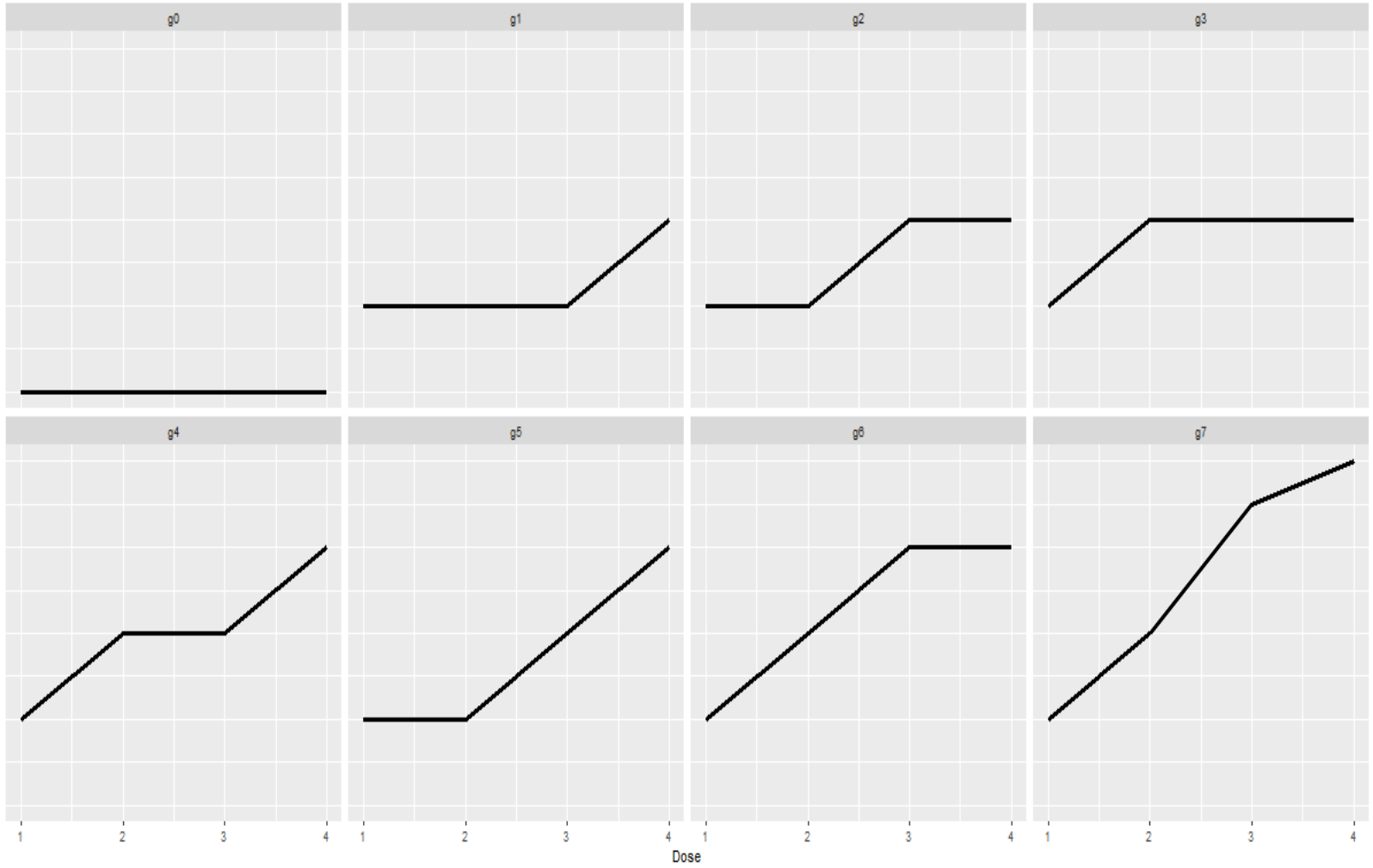
versus

$$H_a\colon \mu_0 \leq \mu_1 \leq \mu_2 \leq \ldots \leq \mu_K$$

All possible models

$$g_0\colon \mu_0 = \mu_1 = \mu_2 = \mu_3$$
$$g_1\colon \mu_0 = \mu_1 = \mu_2 < \mu_3$$
$$g_2\colon \mu_0 = \mu_1 < \mu_2 = \mu_3$$
$$g_3\colon \mu_0 < \mu_1 = \mu_2 = \mu_3$$
$$g_4\colon \mu_0 < \mu_1 = \mu_2 < \mu_3$$
$$g_5\colon \mu_0 = \mu_1 < \mu_2 < \mu_3$$
$$g_6\colon \mu_0 < \mu_1 < \mu_2 = \mu_3$$
$$g_7\colon \mu_0 < \mu_1 < \mu_2 < \mu_3$$

Frequentist approach



2^{K-1} candidate models under order restriction.

There are 8 possible models for K=4 assuming non-decreasing constraint

Frequentist approach

Burnham and Anderson (2002) to fit each of the candidate model and calculate posterior probability of the model given data as:

$$P(g_i|Data) = \frac{P(Data|g_i)P(g_i)}{\sum_{r=1}^{R} P(Data|g_r)P(g_r)} \qquad i = 0, \dots, K-1$$

- Information criteria (IC)
- AIC: Akaike information criterion
- BIC: Bayesian information criterion
- **ORIC: Order restricted information criteria**

Where

$$P(Data|g_r) = e^{-\Delta IC_i} \text{ and } \Delta IC_i = IC_i - \min(IC_1, \dots, IC_{K-1})$$

Bayesian approach

Our main motivation for considering Bayesian approach is to estimate posterior probability for each model under order restriction and to provide framework to simultaneously establish dose-response relationship, dose-response profile and estimate the minimum effective dose

However, there is no direct way to draw posterior samples from order restricted space without strict inequality constraint between parameters.

Bayesian approach

Likelihood

$$Y_{ij} = N(\mu_i, \sigma^2)$$

Prior

$$\mu_i = N\left(\eta_\mu, \sigma_\mu^2\right) I(\mu_{i-1}, \mu_{i+1})$$

(Gelfand and Kuo, 1991)

- Gelfan and Kuo (1991) approach cannot be directly applied when $\mu_{i-1} = \mu_{i+1}$
- Dunson & Nelson (2003) proposed Bayesian isotonic regression.
- Kato and Hoijtink (2006) proposed using encompassing priors.

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Bayesian approach

Dose-response data can be analysed using mixture model with constrained priors. For illustration purpose, let's assume K= 2. A control dose and an active dose.

$$y_i|\mu_0, \delta_1, \sigma^2 = wN(\underbrace{\mu_0 + \delta_1}_{\mu_1 = \mu_0 + \delta_1}, \sigma^2) + (1-w)wN(\underbrace{\mu_0, \sigma^2}_{\mu_1 = \mu_0})$$

- $\mu_1 = \mu_0 + \delta_1$ and $\delta_1 > 0.$
- $\mu_0 \sim N(0, \sigma_1^2)$ and $\delta_1 \sim N(0, \sigma_1^2)I(0,)$
- $\sigma^{-2} \sim IG(0.0001, 0.0001$ and $\sigma_1^{-2} \sim IG(0.0001, 0.0001)$

Kasim *et al.* (2012)

Bayesian approach

The mixture model can be formulated as a Bayesian variable selection model

$$y_i|\mu_0, \delta_1, \sigma^2 = N(\mu_0 + z * \delta_1, \sigma^2)$$

Priors

$$\mu_0 \sim N(0, \sigma_1^2) \qquad z \sim Bern(p)$$

$$\delta_1 \sim N(0, \sigma_1^2) I(0,) \qquad p \sim Unif(0,1)$$

Bayesian approach

Identifier (G=1+$\sum_{h=1}^{K-1} z_h 2^{h-1}$)	Inclusion indicator (z)	Mean Structure	Model label
1	$z = (z_1 = 0, z_2 = 0, z_3 = 0)$	$\mu_0 = \mu_1 = \mu_2 = \mu_3$	g_0
2	$z = (z_1 = 1, z_2 = 0, z_3 = 0)$	$\mu_0 = \mu_1 = \mu_2 < \mu_3$	g_1
3	$z = (z_1 = 0, z_2 = 1, z_3 = 0)$	$\mu_0 = \mu_1 < \mu_2 = \mu_3$	g_2
4	$z = (z_1 = 1, z_2 = 1, z_3 = 0)$	$\mu_0 < \mu_1 = \mu_2 = \mu_3$	g_3
5	$z = (z_1 = 0, z_2 = 0, z_3 = 1)$	$\mu_0 < \mu_1 = \mu_2 < \mu_3$	g_4
6	$z = (z_1 = 1, z_2 = 0, z_3 = 1)$	$\mu_0 = \mu_1 < \mu_2 < \mu_3$	g_5
7	$z = (z_1 = 0, z_2 = 1, z_3 = 1)$	$\mu_0 < \mu_1 < \mu_2 = \mu_3$	g_6
8	$z = (z_1 = 1, z_2 = 1, z_3 = 1)$	$\mu_0 < \mu_1 < \mu_2 < \mu_3$	g_7

BVS automatically compares all the possible models under order restriction constraints.

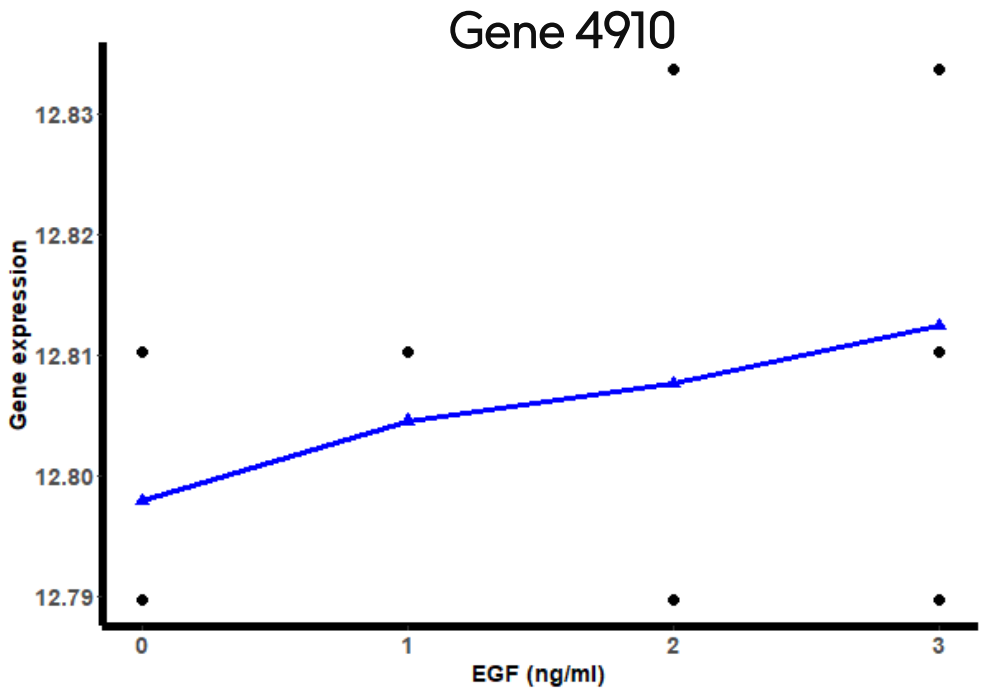
Application to HESCA data

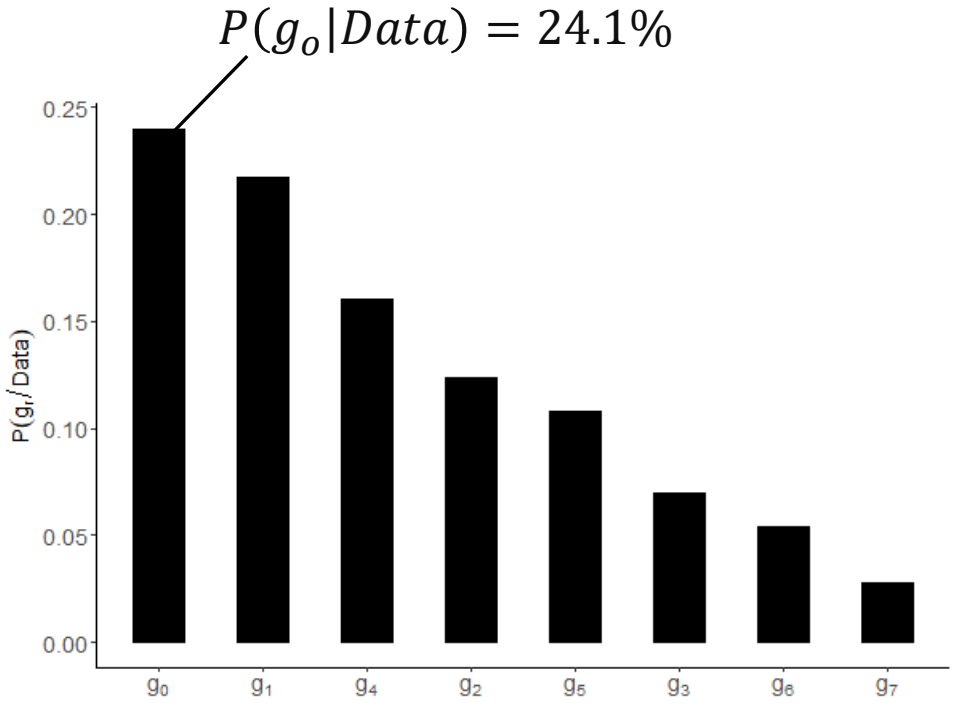
A gene is considered to have a significant dose-response relationship if its posterior probability for the null model ($P(g_0|Data)$) is than a prespecified threshold (α=0.05)

$$P(g_0|Data) < \alpha$$

Otava et al. (2014).

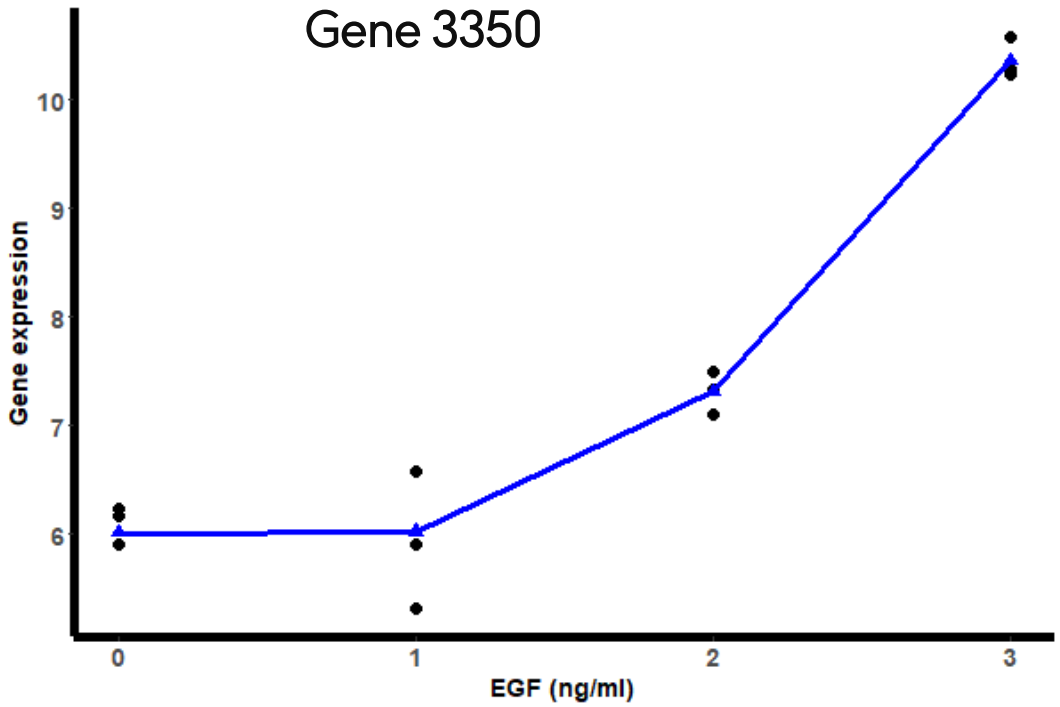
Application to HESCA data

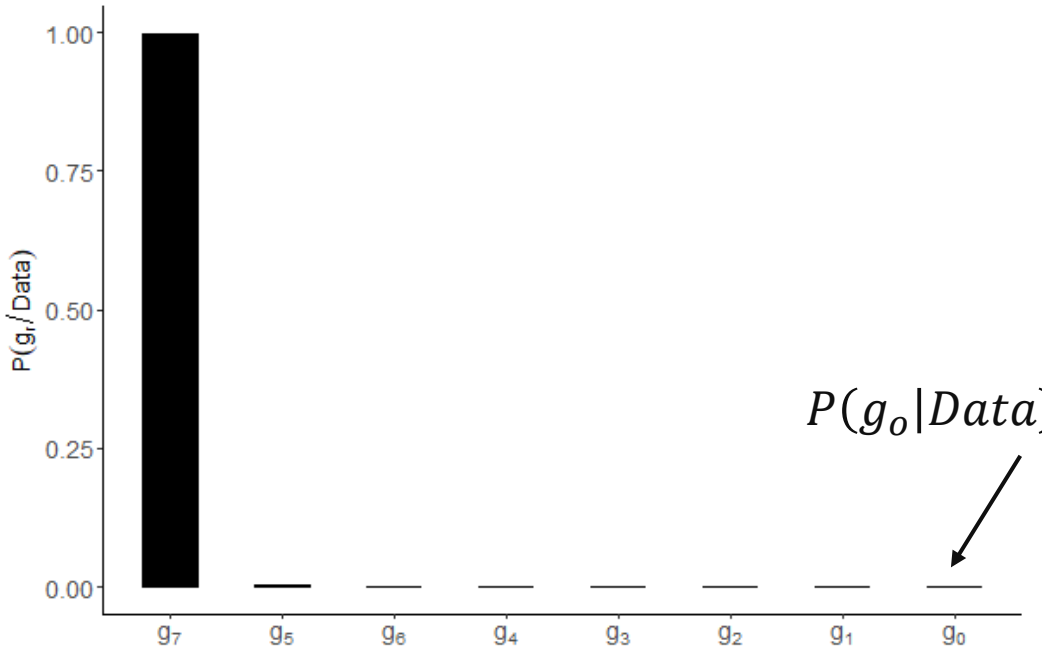




The data does not evidence that increasing dose EGF induces non-decreasing activation of expression level of gene 4910

Application to HESCA data

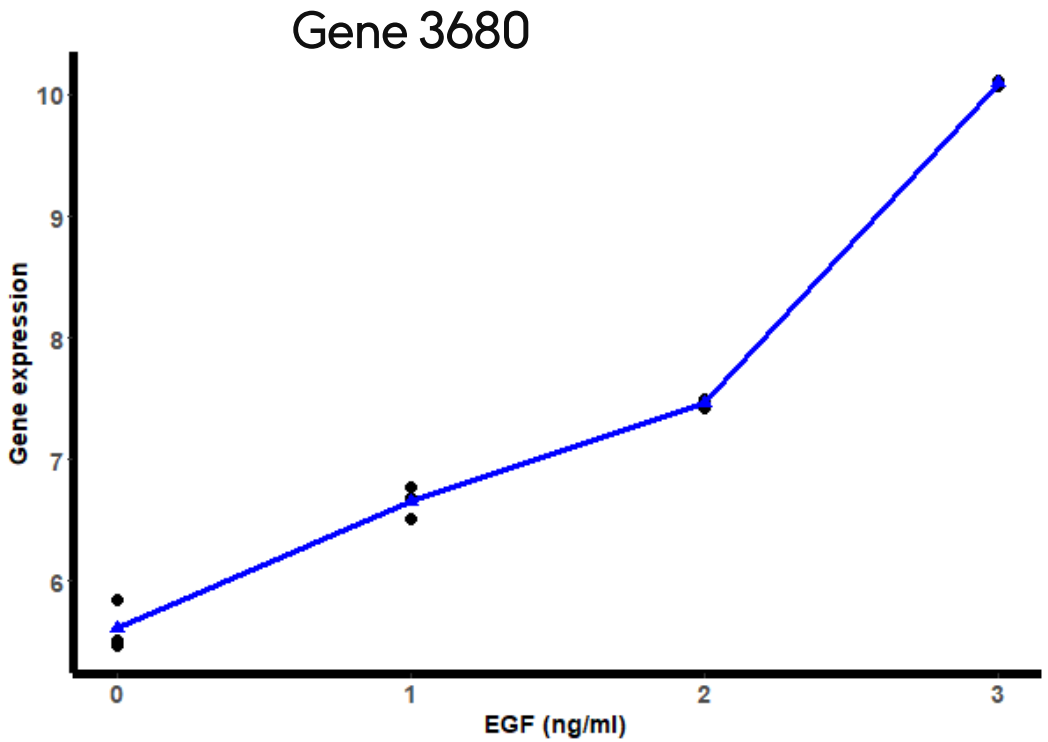


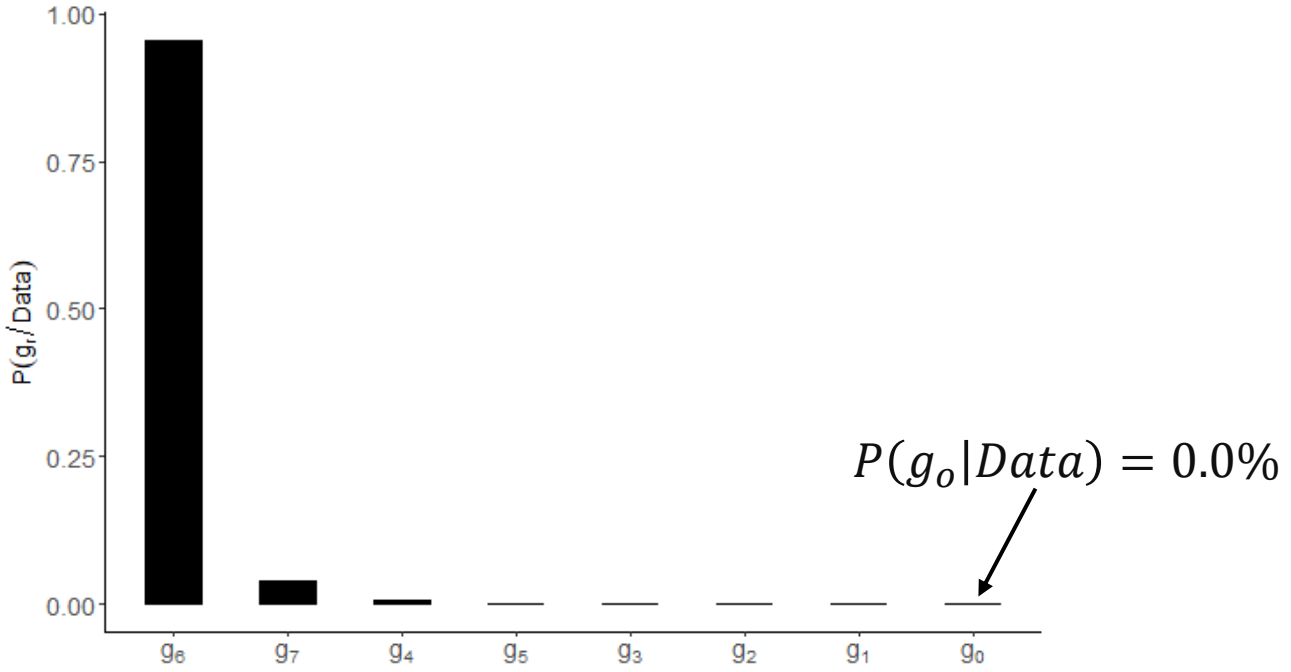


$P(g_o|Data) = 0.0\%$

Increasing dose of EGF induces non-decreasing activation of expression level of gene 3350

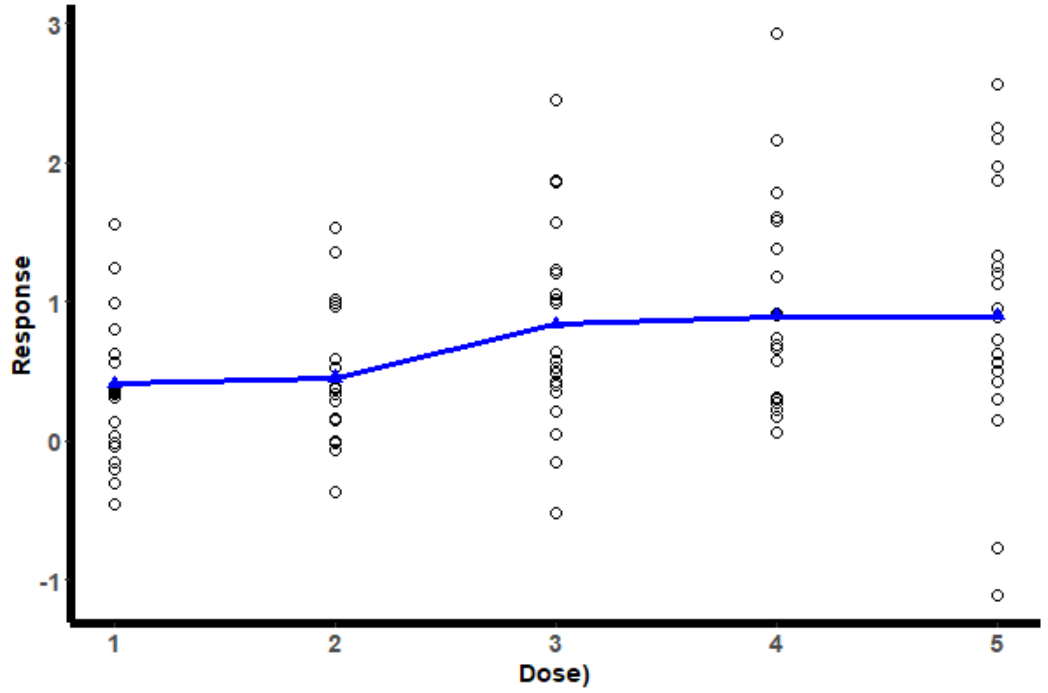
Application to HESCA data

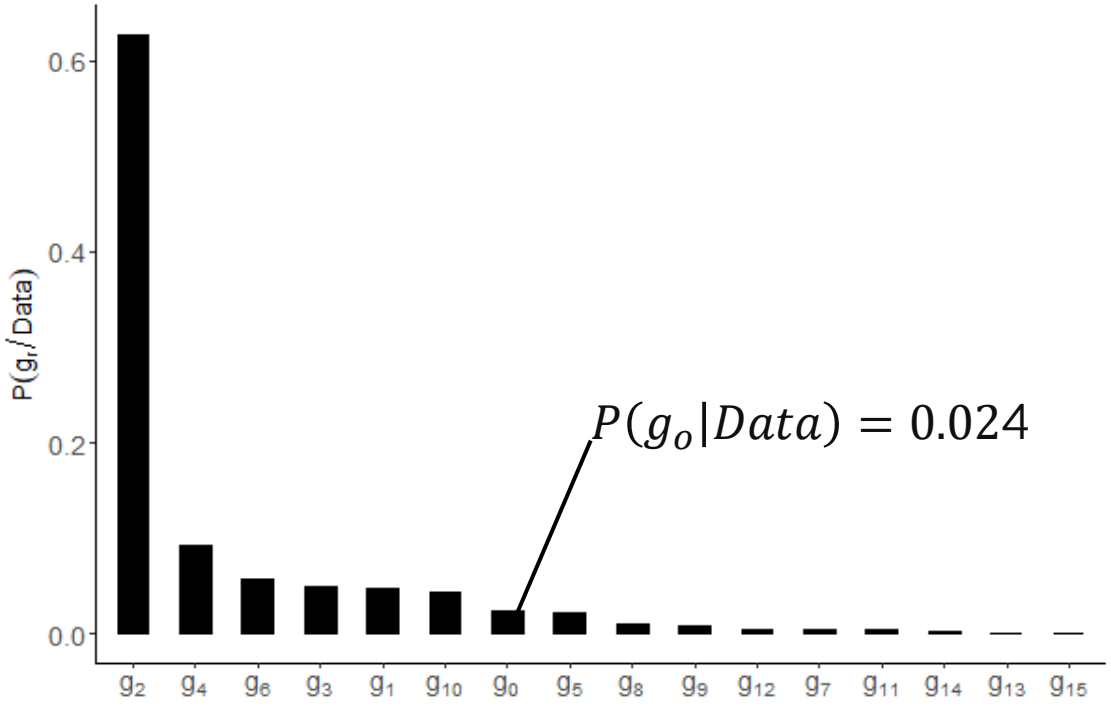




Increasing doses of EGF induced non-decreasing activation of expression level of gene 3350

Application to Biom data





- PoC established $P(g_o|Data) < 0.05$

Application to Biom data

- Bayesian variable selection methods offers an alternative analytical approach to multiple comparison tests and model selection methods
- BVS has higher true positive rate for the same level of false positive rate in comparison with multiple contrasts tests based on William's and Marcus' Test Statistics
- It assumes no parametric functional form between response and dose
- It uses posterior probability to establish to dose response relationship.