Utility-based optimization of phase II / phase III clinical development

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Introduction

Drug Development in Pharmaceutical industries

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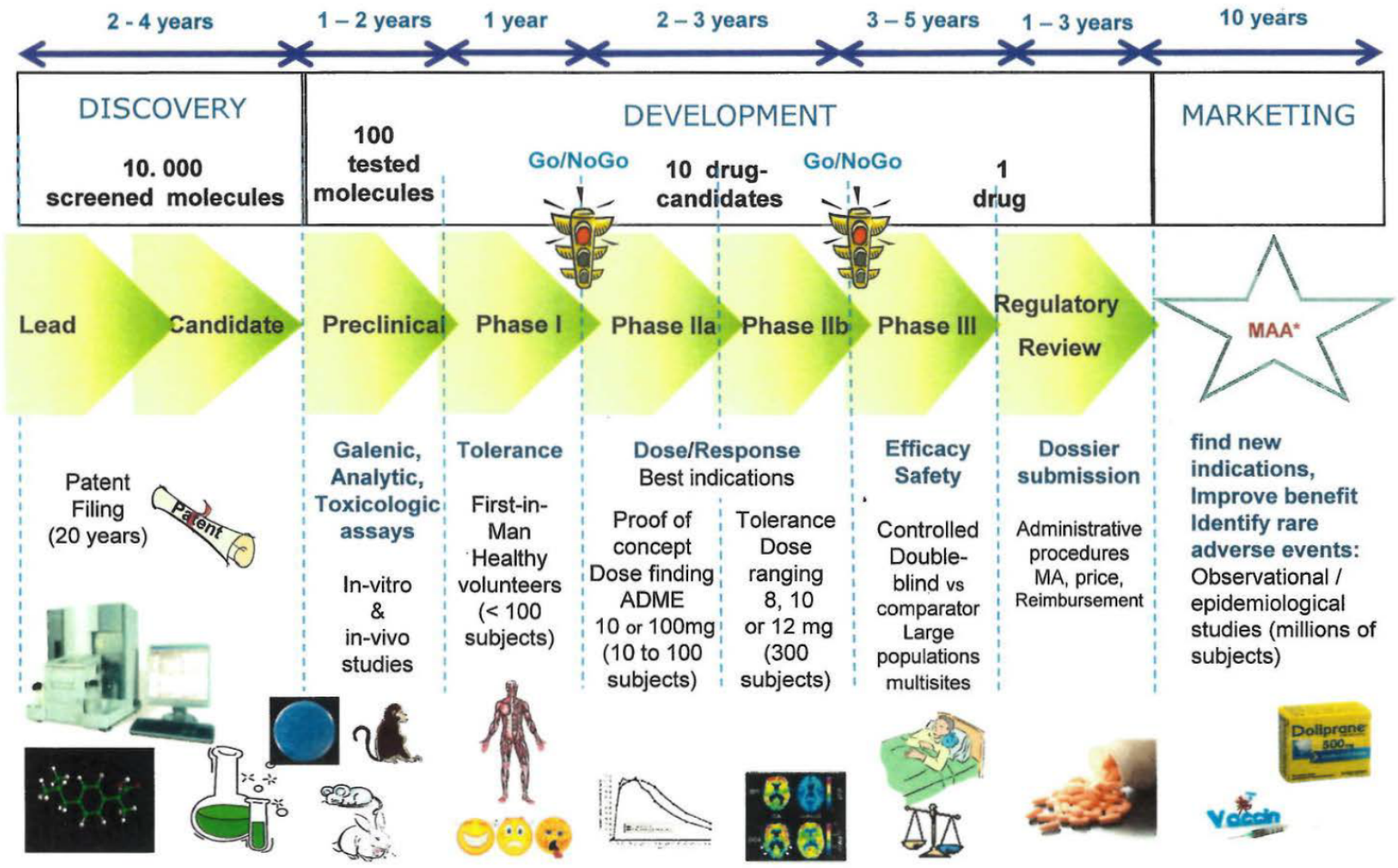
2 - 4 years
1 – 2 years
1 year
2 – 3 years
3 – 5 years
1 – 3 years
10 years
DISCOVERY
10. 000 screened molecules
DEVELOPMENT
100 tested molecules
Go/NoGo
10 drug-candidates
Go/NoGo
1 drug
MARKETING
Lead
Candidate
Preclinical
Phase I
Phase IIa
Phase IIb
Phase III
Regulatory Review
MAA*
Patent Filing (20 years)
Patent
Galenic, Analytic, Toxicologic assays
In-vitro & in-vivo studies
Tolerance
First-in-Man Healthy volunteers (< 100 subjects)
Dose/Response Best indications
Proof of concept Dose finding ADME 10 or 100mg (10 to 100 subjects)
Tolerance Dose ranging 8, 10 or 12 mg (300 subjects)
Efficacy Safety
Controlled Double-blind vs comparator Large populations multisites
Dossier submission
Administrative procedures MA, price, Reimbursement
find new indications, Improve benefit Identify rare adverse events:
Observational / epidemiological studies (millions of subjects)
Doliprane
Vaccin

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Thesis subject

- Dose-finding step is fundamental for phase III in clinical research
- Adaptive designs have already been used in the past and recently in order to select doses
- Optimizing phase II by optimizing the allocation of patients to doses has been poorly explored
  - Several utility functions were proposed and explored through simulations

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Expected goals and objectives of this thesis

1. Phase II objectives / Phase II designs
2. Optimal Design approach
3. Utility Approach

1) Phase II Designs / Objectives

- proof of concept study
  - 1 dose, several doses ?
- if several doses
  - which design: balanced ? or not ?
  - which method of analysis

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2) Optimal Design approach

- D-optimality / C-optimality / Probability of success (POS)
- Multiple doses case and design performance depends of dose response profile, dose of interest
  - Balanced vs optimal design
- Simulations

3) Utility approach

- More flexible than "Optimal designs"
  - enables to account for: safety issues, economical/financial aspects, penalties, ...
- Example of utility functions
  - several doses and a placebo

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Mathematical formalization-Notations

- $Y_{d,i} \sim N(m(d;\theta), \sigma^2)$, $i = 1, ..., n_d$, n_d number of patients per dose group
- Sigmoid-Emax model: $m(d;\theta) = \dfrac{\theta_1 . d^{\theta_3}}{\theta_2^{\theta_3} + d^{\theta_3}}$
  - d is the dose
  - $m(d;\theta)$ is the true effect for dose d
  - $\theta_1 = E_{max}$ is the maximum effect compared with placebo
  - $\theta_2 = ED_{50}$ is the dose with half of the maximum effect
  - $\theta_3 = g$ (or Hill exponent) is a parameter reflecting the shape of the dose-effect curve
- δ is the relative effect: $\delta = \dfrac{m(d;\theta)}{E_{max}} = \dfrac{d^g}{d^g + ED_{50}^g}$
- fixed total sample size: $n_2 + N_3 = N_{total} = constant = 2000$
- f parameter representing patients distribution between phase II and phase III

$n_2 = f \times N_{total}$ and $N_3 = (1 - f) \times N_{total}$

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Utility function example

- $U5 = 1(success) \times (1 - c \times \delta)$
- $U9 = 1(success) \times (1 - c \times (\frac{d_k}{d_{max}})^2)$ (where d_k is the dose and d_{max} is the highest dose)

Sponsor's strategy:

- after phase II:
  - compute $\mathbb{E}(U(d)|phaseII)$ for each dose d
  - compute $d_* = \arg\max_d \mathbb{E}(U(d)|phaseII)$
  - decide if worth going into phase III: if $POS(d_*) \geq 0.30$
- before phase II:
  - choose $n_2 (= f \times N_{tot})$ sample size of phase II
  - choose the design w

$$(w_*) = \arg\max \mathbb{E}_{w,f}^{(phaseII)} \mathbb{E}(U(d_*)|phaseII)$$

or

$$(f_*) = \arg\max \mathbb{E}_{w,f}^{(phaseII)} \mathbb{E}(U(d_*)|phaseII)$$

Probability of success

- success means[1] $\bar{\Delta}(d) \geq 1.96 \times \sqrt{2SE^2}$ (with $SE^2 = s^2/(N_3/2) = 2s^2/N_3$ and $\bar{\Delta}(d)$ is the difference between the dose and the placebo after phase III)
- true POS:

$$POS = \mathbb{P}(\bar{\Delta}(d) \geq 1.96 \times \sqrt{2SE^2}) = \Phi\left(\frac{m(d;\theta_0) - 1.96 \times \sqrt{2SE^2}}{\sqrt{2SE^2}}\right)$$

- POS computed by sponsor for dose selection; uses the point estimate:

$$POS = \Phi\left(\left(m(d;\hat{\theta}) - 1.96 \times \sqrt{2SE^2}\right)/\sqrt{2SE^2}\right)$$

[1] the residual variability,s, is assumed to be known and is set to 0.5 in the simulations

Computation of expectation

$\mathbb{E}(U(d_*)|phaseII)$ is a function, $\mathcal{U}$, of $\hat{\theta} \Rightarrow$
$\mathbb{E}_{w,f}^{(phaseII)}\mathbb{E}(U(d_*)|phaseII) = \mathbb{E}^{(\hat{\theta})}\mathcal{U}(\hat{\theta})$ with $\hat{\theta} \sim N(\theta_0, \mathcal{I}_{\theta_0}^{-1})$

Then $\mathbb{E}_{w,f}^{(phaseII)}\mathbb{E}(U(d_*)|phaseII)$ estimated by:

$$\frac{1}{N_{sim}}\sum_{r=1}^{N_{sim}}\mathcal{U}(\hat{\theta}_r)$$

where the $\hat{\theta}_r$ are sampled from $N(\theta_0, \mathcal{I}_{\theta_0}^{-1})$

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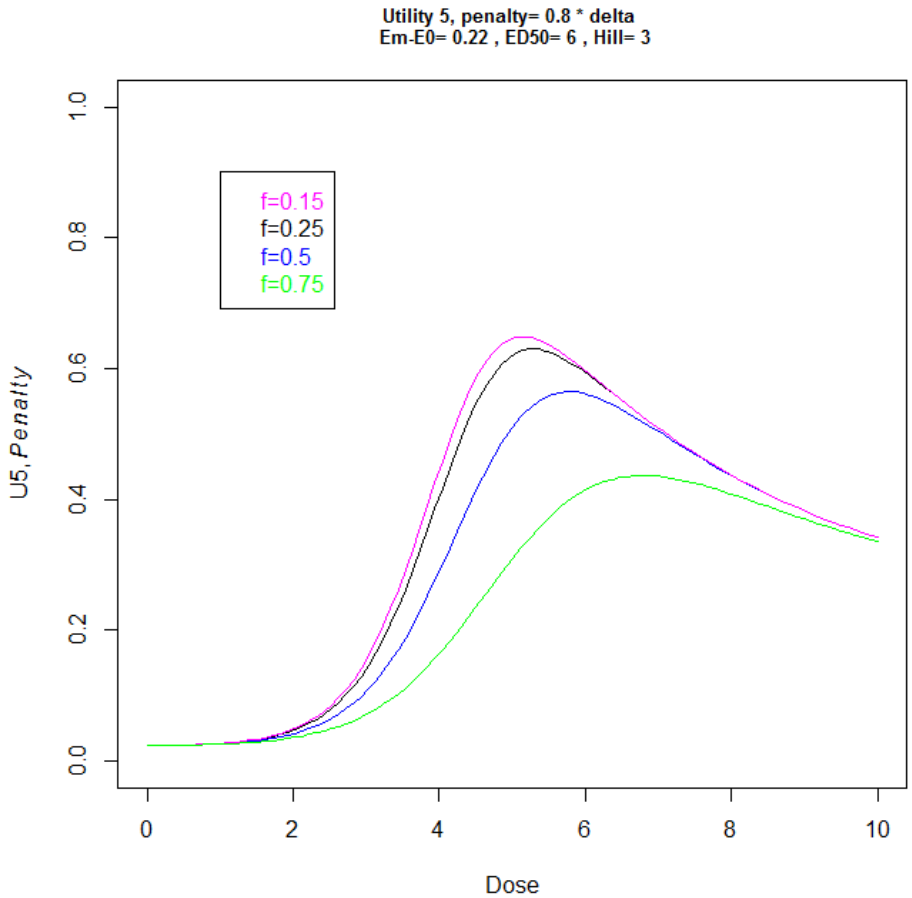
"Theoretical" Utility 5 depends on the size of the phase III:



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$$U9 = 1(success) \times (1 - c \times (d_k / d_{max})^2)$$

Dose 2
True value : 0.0079
Estimated value → summary(compile$estd2)

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.00000	0.00769	0.02652	0.56800	0.12700	165.60000

Dose 4
True value : 0.0503
Estimated value → summary(compile$estd4)

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.00000	0.03095	0.06719	0.62000	0.19460	166.00000

Dose 6
True value : 0.11
Estimated value → summary(compile$estd6)

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.0000	0.0467	0.1055	0.6585	0.2459	166.2000

Dose 8
True value : 0.1547
Estimated value → summary(compile$estd8)

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.00000	0.05419	0.13660	0.68820	0.29060	166.40000

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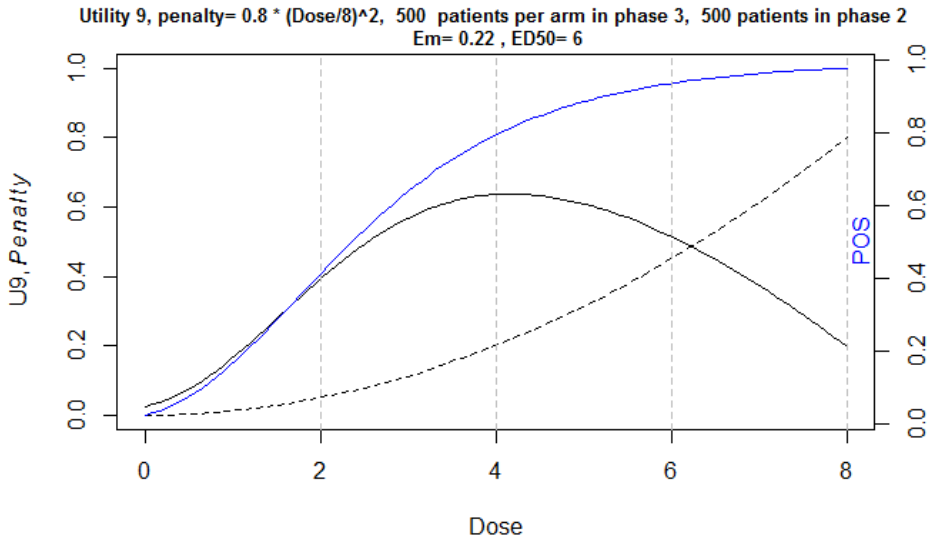
$\Rightarrow$ Remove the 'Hill' exponent g:



According to the 15000 simulations with the two parameter model (E_{max}, ED_{50}):

- Prob(go)=0.77
- Prob(choosing dose 2)=7.4%
- Prob(choosing dose 4)=59.40%
- Prob(choosing dose 6)=27.34%
- Prob(choosing dose 8)=5.82%

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d=2 true value -> 0.055

estimate

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.0002888	0.0221700	0.0392300	0.0401700	0.0552400	0.1432000

d=4 true value -> 0.088

estimate

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.0002888	0.0343100	0.0581000	0.0591200	0.0802100	0.2096000

d=6 true value -> 0.11

estimate

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.0002888	0.0426600	0.0714500	0.0729400	0.0988600	0.2648000

d=8 true value -> 0.12

estimate

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.0002888	0.0486200	0.0823000	0.0840500	0.1140000	0.3049000

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- Effects are not very well estimated when "Hill" exponent was removed
- However, 'theta' is fairly well estimated, we have:
  - Theta.true: $log(E_m) = -1.514128$ and $log(ED_{50}) = 1.791759$
  - Mean estimate: $log(E_m) \rightarrow -1.52357$ and $log(ED_{50}) \rightarrow 1.780353$

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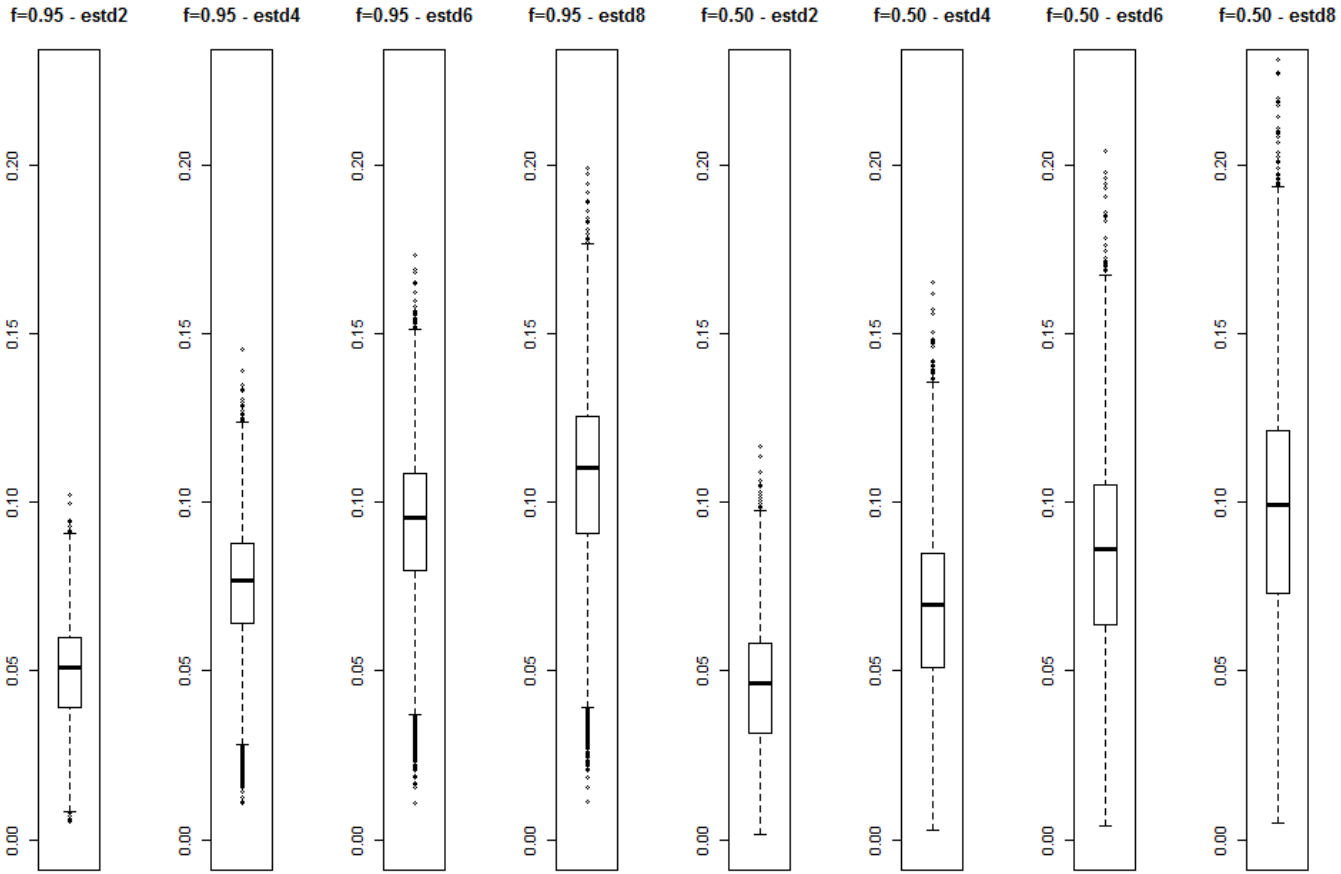
f=0.95 - estd2
f=0.95 - estd4
f=0.95 - estd6
f=0.95 - estd8
f=0.50 - estd2
f=0.50 - estd4
f=0.50 - estd6
f=0.50 - estd8
0.00
0.05
0.10
0.15
0.20

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Non Optimal Designs

Point 2			
Emax 2 parameters	**U9_2param**	**Sigmoid1**	**Plateau**
		w=(0.2,0.2,0.2,0.2,0.2),f=0.10	w=(0.2,0.2,0.2,0.2,0.2),f=0.10
		Go=55%	Go=69%
		doses=0.16 0.47 0.28 0.09	doses=0.65 0.22 0.09 0.04
		POS(go)=79%	POS(go)=90%
		E(U)=0.2884105	E(U)=0.5211206
		w=(0.2,0.2,0.2,0.2,0.2),f=0.25	w=(0.2,0.2,0.2,0.2,0.2),f=0.25
		Go=78%	Go=88%
		doses=0.08 0.60 0.27 0.05	doses=0.63 0.25 0.09 0.03
		POS(go)=81%	POS(go)=90%
		E(U)= 0.436873	E(U)=0.6665605
		w=(0.2,0.2,0.2,0.2,0.2),f=0.50	w=(0.2,0.2,0.2,0.2,0.2),f=0.50
		Go=91%	Go=96%
		doses=0.04 0.68 0.24 0.03	doses=0.61 0.30 0.08 0.02
		POS(go)=82%	POS(go)=90%
		E(U)=0.5274331	E(U)=0.7395557

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Optimal Designs

Point 2			
Emax 2 parameters	**U9_2param**	**Sigmoid1**	**Plateau**
		w=(0.00,0.63,0.03,0.00,0.33),f=0.10	w=(0.00,0.46,0.01,0.02,0.51),f=0.10
		Go=72%	Go=84%
		doses= 0.13 0.52 0.27 0.07	doses= 0.62 0.25 0.10 0.03
		POS(go)=79%	POS(go)=90%
		E(U)= 0.3874309	E(U)= 0.6358422
		w=(0.00,0.65,0.06,0.00,0.34),f=0.25	w=(0.19,0.21,0.19,0.20,0.21),f=0.25
		Go=91%	Go=88%
		doses= 0.06 0.66 0.24 0.03	doses= 0.62 0.26 0.09 0.03
		POS(go)=81%	POS(go)=90%
		E(U)= 0.526404	E(U)= 0.672623
		w=(0.02,0.68,0.03,0.00,0.27),f=0.50	w=(0.06,0.52,0.01,0.03,0.38),f=0.50
		Go=98%	Go=100%
		doses= 0.02 0.79 0.19 0.01	doses= 0.64 0.32 0.04 0.00
		POS(go)=82%	POS(go)=90%
		E(U)= 0.5921385	E(U)= 0.7839223

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New Steps

- Global patient allocation between phase II and phase III optimization, rather than dose allocation optimization
- Focus on $U9 = 1(success) \times (1 - c \times (\frac{d_k}{d_{max}})^2)$
- 3-parameter model (E_0, $log(ED_{50})$ and $log(E_m)$)
- Include a second constraint in the decision rule: the POS must be > 0.3 and the effect difference between placebo and the recommended dose must be > 0.04

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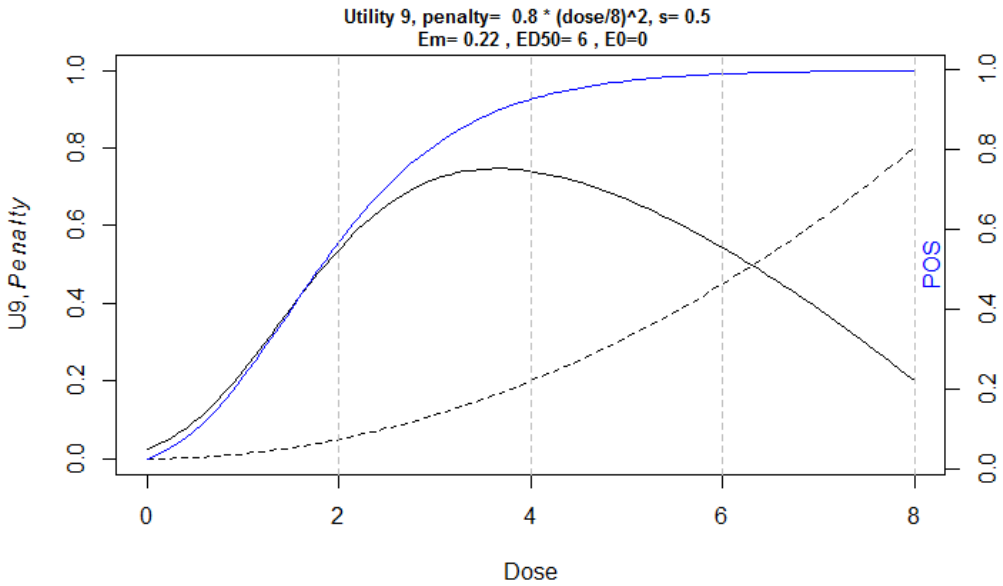
New results


Utility 9, penalty= 0.8 * (dose/8)^2, s= 0.5
Em= 0.22 , ED50= 6 , E0=0
U9, Penalty
POS
Dose
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8

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Probability results of selecting each dose, as well as the probability of 'Go':

- Prob(Go)=0.7352667
- Prob(choosing dose 2)=32.13347
- Prob(choosing dose 4)=40.39351
- Prob(choosing dose 6)=20.93571
- Prob(choosing dose 8)=6.537311

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Descriptive statistics of the estimates (E_0, $log(E_m)$ and $log(ED_{50})$):

```
> summary(U9_simul_complet$X1)    log(Em): true value= -1.514128
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
-7.6495 -2.4701 -1.5130 -1.5164 -0.5561  3.7237
> summary(U9_simul_complet$X2)    log(ED50): true value=1.791759
    Min.  1st Qu.   Median     Mean  3rd Qu.    Max.
-12.2139  -0.2554   1.8198   1.7958   3.8761  13.3549
> summary(U9_simul_complet$X3)    E0 : true value=0
     Min.    1st Qu.    Median      Mean    3rd Qu.      Max.
-1.858e-01 -3.334e-02  1.242e-04 -5.821e-05  3.365e-02  1.854e-01
```

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Descriptive statistics of the dose effects (dose d versus placebo):

```
> summary(U9_simul_complet$estd2)  0.07
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
0.0000912 0.0167214 0.0345835 0.0434328 0.0598453 0.4160290
> summary(U9_simul_complet$estd4)  0.09
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
0.0001824 0.0263163 0.0509724 0.0619272 0.0839857 0.5185502
> summary(U9_simul_complet$estd6)  0.11
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
0.0002736 0.0331183 0.0621437 0.0751841 0.1011619 0.5697685
> summary(U9_simul_complet$estd8)  0.12
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
0.0003648 0.0380519 0.0708128 0.0857639 0.1153829 0.6130136
```

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Non Optimal

	Sigmoid1	Plateau
f=0.10	w = (0.2,0.2,0.2,0.2,0.2) Go=51% doses= 0.44, 0.32, 0.17, 0.07 POS(go)=83% POS(global)=42.3% E(U)= 0.315097	w = (0.2,0.2,0.2,0.2,0.2) Go=66% doses=0.74, 0.16, 0.07, 0.03 POS(go)=99% POS(global)=65.3% E(U)= 0.568064
f=0.25	w = (0.2,0.2,0.2,0.2,0.2) Go=74% doses= 0.32, 0.41, 0.21, 0.06 POS(go)=83% POS(global)=61.4% E(U)= 0.4435682	w = (0.2,0.2,0.2,0.2,0.2) Go=86% doses= 0.69, 0.21, 0.08, 0.03 POS(go)=97% POS(global)=83.4% E(U)= 0.7211123
f=0.50	w = (0.2,0.2,0.2,0.2,0.2) Go=86% doses= 0.17, 0.52, 0.25, 0.05 POS(go)=77% POS(global)=66.2% E(U)= 0.4625786	w = (0.2,0.2,0.2,0.2,0.2) Go=94% doses= 0.61, 0.29, 0.08, 0.02 POS(go)=90% POS(global)=84.6% E(U)= 0.7178017

Optimal

Sigmoid1	Plateau
w = (0.2,0.2,0.2,0.2,0.2), f=0.4008782 Go=83% doses= 0.23, 0.49, 0.23, 0.05 POS(go)=80% POS(global)=66.4 E(U)= 0.4778065	w = (0.2,0.2,0.2,0.2,0.2), f=0.3775344 Go=92% doses=0.65, 0.25, 0.08, 0.02 POS(go)=95% POS(global)=87.4 E(U)=0.745277

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Conclusion and Perspectives

Main findings:

- Optimizing the dose allocation ratio in stage 2 of the dose-finding study offers very little improvement in regard of significantly increased operational complexity and consequently, this optimization part was removed from the scope of this thesis
- Utility functions depending on the parameters of the dose-response function make things complicated $\rightarrow$ increase in uncertainty and bad choices after phase II, therefore it is better to reduce the number of parameters in the model
- The sample size of phase II is vital: it is better to have quite enough patients in phase II to make a better choice

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Perspectives:

- Put uncertainty on the penalty of toxicity and rework it properly
- c coefficient mustn't be constant
- c coefficient should become a prior law on the tolerance percentage of a given dose by patients, where tolerance is defined by following the treatment to the end

So the idea here is to put efficacy and safety at the same level and avoid arbitrary choices for toxicity:

- Characterize subject's safety by using a binary safety outcome mimicking the drug limiting toxicity (DLT) concept
- Penalty considered for each subject would depend on the expected probability of DLT / treatment discontinuation at the given dose
- Optimizing the patient allocation ratio between phase II and phase III

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Appendices

Mathematical formalization of a Phase II clinical trial I

- $Y_{d,t}$ data represeting patients treated with dose d for different stages, where $t \in \{1, 2, 3\}$
- $Dose_0$ and $Dose_t$ the set of selected doses
- D is the decision rule
- F is the data probabilistic model given the parameters
- $\theta_d \rightarrow$ parameter (efficacy of dose d)
- $Y_{d,t} \sim F(\theta_d, d)$ where $d \in Dose_t$
- $X_t = \{Y_{d,1}, ..., Y_{d,t}, Dose_0, ..., Dose_t\}$ set of observed data and doses
- $D_t : \chi \longrightarrow w$
- We select the allocation ratio for the next group according to the D function
- In other words, we have two main steps:
  - Decision step: $X_t \longrightarrow w_t = D_t(X_t)$, where $t \in \{1, 2\}$
  - Hazard step: $X_{t+1} = U_t(X_t, D_t(X_t), Y_{d,t})$, where $Y_{d,t} \sim F(\theta_d, d)$

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Examples of utility functions I

1. $U1 = -\gamma N_T + 1(success) \times (R - c(d^g/(ED_{50}^g + d^g) - 0.95)^2)$
2. $U2 = -\gamma N_T + 1(success) \times R_{max}(1 - \delta)$
3. $U3 = -\gamma N_T + 1(success) \times R_{max}(1 - \delta)^2$
4. $U4 = 1(success) \times (1 - c(d^g/(ED_{50}^g + d^g) - 0.95)^2)$ (without $-\gamma N_T$ and R)
5. $U5 = 1(success) \times (1 - c \times \delta)$
6. $U6 = 1(success) \times (1 - c \times \delta)^2$ (without $-\gamma N_T$ and R)
7. $U7 = -\gamma N_T + 1(success) \times (R - 1.c(d^g/(ED_{50}^g + d^g) - 0.95)^2)$ (where 1. is an indicator which doesn't allow to take into account the quantity "$c(d^g/(ED_{50}^g + d^g) - 0.95)^2$" unless we exceed ED_{95})

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Examples of utility functions II

8. $U8 = 1(success) \times (1 - 1.c(d^g/(ED_{50}^g + d^g) - 0.95)^2)$ (without $-\gamma N_T$ and R, where 1. is an indicator which doesn't allow to take into account the quantity "$c(d^g/(ED_{50}^g + d^g) - 0.95)^2$" unless we exceed ED_{95})
9. $U9 = 1(success) \times (1 - c \times (\frac{d_k}{d_{max}})^2)$ (where d_k is the dose and d_{max} is the highest dose)

Reminder: $\delta = d^g/(ED_{50}^g + d^g)$ *and the 1. indicator is mathematically translated by* $1(\frac{d^g}{ED_{50}^g + d^g} > 0.95) = 1$ *if* $\frac{d^g}{ED_{50}^g + d^g} > 0.95$ *and* $= 0$ *if* $\frac{d^g}{ED_{50}^g + d^g} \leq 0.95$.

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Examples of utility functions III

- Focus on two utility functions: $U5$ and $U9$
- Computational and optimization problems $\rightarrow$ move away from Bayesian context
- Analyse phase II with a parametric model (E_{max} with a parameter θ)

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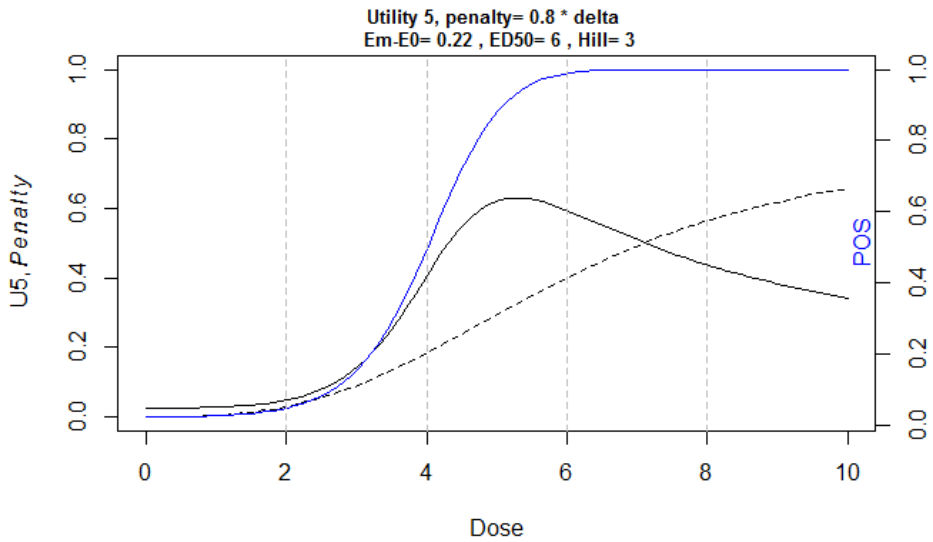
$$U5 = 1(success) \times (1 - c \times \delta)$$



Non optimal

sigmoid1	plateau
w = (0.2,0.2,0.2,0.2,0.2), f = 0.25 Go=:63% doses= 0.47, 0.21, 0.19, 0.14 POS(go)=45% E(U)= 0.1600304	w = (0.2,0.2,0.2,0.2,0.2), f = 0.25 Go=94% doses= 0.66, 0.21,0.04, 0.09 POS(go)=90% E(U)= 0.40004825

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Optimal design

sigmoid1	Plateau
w = (0.21,0.21,0.21,0.19,0.18), f = 0.25 Go=:63% doses= 0.46, 0.22, 0.18, 0.14 POS(go)=45% E(U)= 0.1638747	w = (0.22,0.18,0.19,0.21,0.20), f = 0.25 Go=:94% doses= 0.65, 0.21, 0.05, 0.09 POS(go)=90% E(U)= 0.3996662

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- Probability to go to phase III = 63.2%
- Probality of choosing dose 2, if go, = 46.6078916%
- Probality of choosing dose 4, if go, = 20.9224815%
- Probality of choosing dose 6, if go, = 18.9657026%
- Probality of choosing dose 8, if go, = 13.5039243%

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sigmoid1

w = (0.2,0.2,0.2,0.2,0.2), f = 0.25
Go=:63%
doses= 0.47, 0.21, 0.19, 0.14
POS(go)=45%
E(U)= 0.1600304

sigmoid1

w = (0.2,0.2,0.2,0.2,0.2), f = 0.50
Go=:68%
doses=0.27, 0.23, 0.31, 0.19
POS(go)=57%
E(U)= 0.2202242

sigmoid1

w = (0.2,0.2,0.2,0.2,0.2), f = 0.75
Go=70%
doses= 0.12, 0.11, 0.37, 0.41
POS(go)=66%
E(U)= 0.2210461

sigmoid1

w = (0.2,0.2,0.2,0.2,0.2), f = 0.95
Go=:44%
doses= 0.01, 0.00, 0.03, 0.96
POS(go)=33%
E(U)= 0.06320928

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By increasing the phase II, by taking $n_2 = 2000$ patients, and keeping $N_3 = 1500$ patients, we obtain:

- Prob(dose 2) $= 17\%$
- Prob(dose 4) $= 36\%$
- Prob(dose 6) $= 41\%$
- Prob(dose 8) $= 9\%$

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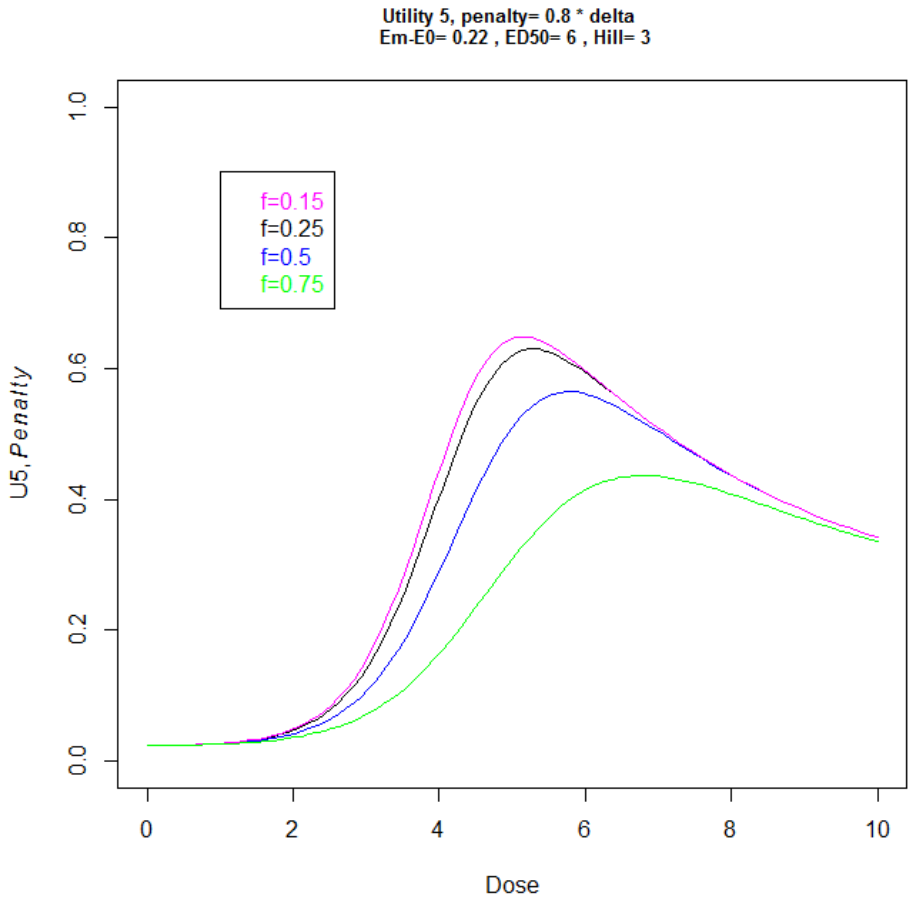
"Theoretical" utility depends on the size of the phase III:



With no modeling approach (simulate the stage 1 of phase II, without simulating all the patients, one can simulate a mean and a variance per dose group, for example $\bar{x} \sim N(\mu_2, \frac{s}{n_2})$, where μ_2 is the empirical mean for the dose 2 group, s is the residual variance, and n_2 is the number of patients for this dose 2 group), we have the following results:

- Prob(go)=0.96
- Prob(choosing dose 2)=38.6%
- Prob(choosing dose 4)=38.5%
- Prob(choosing dose 6)=18.3%
- Prob(choosing dose 8)=4.7%

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Simulated means are consistent with theoretical means:

```
Placebo > summary(U9_simul_complet$X1)
      Min.    1st Qu.     Median       Mean    3rd Qu.       Max.
-0.1829000 -0.0343400 -0.0007815 -0.0008171  0.0328200  0.2141000

Dose 2 > summary(U9_simul_complet$X2)
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
-0.13830  0.01995  0.05359  0.05351  0.08699  0.25770

Dose 4 > summary(U9_simul_complet$X3)
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
-0.09561  0.05504  0.08896  0.08892  0.12350  0.28900

Dose 6 > summary(U9_simul_complet$X4)
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
-0.11750  0.07646  0.11000  0.10970  0.14320  0.29400

Dose 8 > summary(U9_simul_complet$X5)
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
-0.08588  0.09172  0.12570  0.12560  0.15900  0.33680
```

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Point 3			
No Model	**U9_non_param**	**Sigmoid1**	**Plateau**
		w=(0.2,0.2,0.2,0.2,0.2),f=0.10	w=(0.2,0.2,0.2,0.2,0.2),f=0.10
		Go=92%	Go=95%
		doses=0.48 0.30 0.16 0.06	doses=0.61 0.26 0.10 0.04
		POS(go)=65%	POS(go)=90%
		E(U)=0.4361716	E(U)=0.7124915
		w=(0.2,0.2,0.2,0.2,0.2),f=0.25	w=(0.2,0.2,0.2,0.2,0.2),f=0.25
		Go=96%	Go=98%
		doses=0.39 0.37 0.18 0.05	doses=0.61 0.29 0.09 0.02
		POS(go)=68%	POS(go)=90%
		E(U)=0.4759959	E(U)= 0.7486909
		w=(0.2,0.2,0.2,0.2,0.2),f=0.50	w=(0.2,0.2,0.2,0.2,0.2),f=0.50
		Go=99%	Go=99%
		doses=0.33 0.44 0.20 0.03	doses=0.63 0.30 0.06 0.01
		POS(go)=70%	POS(go)=90%
		E(U)=0.5090461	E(U)=0.7748988

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Point 3			
No Model	**U9_non_param**	**Sigmoid1**	**Plateau**
		w=(0.59,0.08,0.09,0.13,0.11),f=0.10	w=(0.23,0.19,0.20,0.19,0.19),f=0.10
		Go=97%	Go=95%
		doses= 0.46 0.33 0.16 0.05	doses= 0.61 0.26 0.10 0.03
		POS(go)=65%	POS(go)=90%
		E(U)= 0.4713943	E(U)= 0.7180307
		w=(0.48,0.12,0.14,0.13,0.13),f=0.25	w=(0.2,0.2,0.2,0.2,0.2),f=0.25
		Go=99%	Go=99%
		doses= 0.39 0.40 0.18 0.03	doses= 0.61 0.29 0.09 0.02
		POS(go)=68%	POS(go)=90%
		E(U)= 0.4980988	E(U)= 0.7566064
		w=(0.23,0.19,0.19,0.18,0.20),f=0.50	w=(0.55,0.25,0.10,0.07,0.03),f=0.50
		Go=99%	Go=100%
		doses= 0.33 0.44 0.20 0.03	doses= 0.65 0.30 0.05 0.00
		POS(go)=70%	POS(go)=89%
		E(U)= 0.5139042	E(U)= 0.7858431

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By considering $w = c(0.06, 0.52, 0.01, 0.03, 0.38)$ as a starting value for the algorithm:

Plateau
w=(0.17,0.28,0.016,0.015,0.25),f=0.25
Go=91%
doses= 0.62 0.27 0.09 0.02
POS(go)=90%
E(U)= 0.6961431

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Utility definitions

- With or without economic consideration (i.e. costs, phase II & phase III, potential gains if success)
- This type of utility, $U = 1 \times Penalty$, if successful, 0, otherwise, was privileged:
  - The dose that maximizes the average utility is the one that maximizes $\mathbb{E}\mathbf{1}(success) \times Penalty(dose, \theta) = POS(dose, \theta, N_3) \times Penalty(dose, \theta)$
  - The sponsor chooses, after phase II, the dose with the average utility estimation: $POS(dose, \hat{\theta}, N_3) \times Penalty(dose, \hat{\theta})$
- It is better to avoid a penalty depending on the model (on θ)
  - Moreover, if the sponsor has a constant total number, as soon as the molecule is a little efficient, the sponsor has an interest in putting as many patients as possible in phase III so that the low dose has a POS close to 1 (even if the effect is very small), and since the penalty is minimal for the low dose $\Rightarrow$ the low dose will be optimal

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