

# On the use of utility functions for optimizing phase II/phase III seamless trial designs

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## Abstract

### Background:

For several years adaptive designs became more and more popular in the pharmaceutical industry and in particular much attention was brought on adaptive seamless designs. Those designs combine the phase II dose finding trial and the phase III confirmatory trial in a single protocol (with a fixed total sample size). The objective of this paper is to propose some utility-based tools to optimize those designs: first in terms of ratio between phase II and phase III sample sizes, and, second, in patient allocation to doses at the beginning of phase II.

### Methods:

Design optimization methods are generally based either on Fisher information matrix (D-optimality) or on the variance of some statistics of interest (C-optimality). Instead, we propose to define utility functions associated to sponsors' decision related to choice of dose for the phase III and we propose design optimization metrics based on the expected value of this utility.

### Results and Conclusions:

After reviewing and discussing several kinds of utility functions, we focused on two of them, that we have assessed through simulations. We concluded that in most of the scenarios simulated, the expected utility was in a sense more sensitive to the timing of the interim analysis (ratio between phase II over total sample size) than on the patients allocation between the doses. This result points out the fact that it might be necessary to enroll a larger number of patients in phase II to allow an accurate identification of the optimal dose.

*Keywords: Adaptive trials; Design optimisation; Dose selection; Patient allocation; Seamless design; Utility function*

This article does not contain any studies with human or animal subjects performed by any of the authors.

## 1 Introduction

### 1.1 Methodologies for dose selection in drug development

The choice of the dose for the phase III is a key milestone of the drug development [1]. Therefore the methodology attached to the design, and the analysis of the dose-finding study as well as for the dose-selection rule is of major importance.

Traditionally, apart from oncology indication, the search of the optimal dose resulted from a sequential process: first the set of efficacious doses (it could include only one dose or in the worst case scenario, none) was identified and second, the highest dose considered as "safe" or "well tolerated" was selected for the late development phases. Also, the first step related to the identification of the efficacious doses were driven by multiple-testing procedures: the set of efficacious doses was defined as the set of doses that were significantly different from placebo in the dose finding study after adjustment for multiplicity. Various multiple-testing procedures can be considered: Dunnett's procedure is widely used for the quantitative variables, more recent general gatekeeping procedures [2] are also used.

A more recent approach that requires the assessment of the dose-response (for efficacy) relationship is the Multiple Comparison Procedure and Modeling (MCP-Mod) [3]. It uses a predefined set of candidate models for the dose-response relationship. Once the evidence of a drug effect is established at the MCP step using multiple contrast tests, a Mod step is used to estimate the dose meeting the expectations of the sponsor.

It is now becomingly accepted that finding the right dose should be rather considered as an estimation problem than a multiple testing problem [4]. This latter traditional approach, as well as the more recent MCP-Mod procedures generally consider efficacy and safety sequentially: doses associated with statistically significant differences versus the control, for the multiple testing approach, or doses with desired difference versus control, for the MCP-Mod approach, are identified first and then the highest dose amongst them considered as "well tolerated" is generally chosen. This is the approach we have selected in this paper, in formalizing the decision rule with the help of utility functions.

## 1.2 Designs for dose-finding studies: fixed and adaptive designs studies

The standard dose finding study is parallel arms study with 4 or 5 doses and a control group (in general a placebo group) with a balanced design. Seamless designs, combining both phase II (dose-finding) and phase III trials, are becoming increasingly important [5];[6];[7]. The problem of optimizing the design for the purpose of dose selection has already been addressed (see for example [8] where the aim is to establish efficient study designs to estimate relevant target doses) but the methodology is most often based on C-optimality (based on the variance of some statistics of interest) or D-optimality (based on Fisher information matrix). Some work dedicated to the optimisation of designs based on utility functions exist but they are rather sparse: we can mention [9], in which the design is optimized by minimizing the expectation of a cost, or [10];[11];[12];[13], in which the optimisation of stage 2 by optimizing patients allocation is addressed. But as of today, one lacks of a unified framework based on Decision Theory aimed at assessing and comparing several dose-finding strategies and designs. Instead of using classical design optimization (D-optimality or C-optimality), we propose to define utility functions associated to sponsors' decision related to choice of dose for the phase III and we propose design optimization metrics based on the expected value of this utility. More specifically, the objective of this paper is to propose some utility-based tools to optimize seamless designs: first in terms of ratio between phase II and phase III sample sizes, and, second, in patient allocation to doses at the beginning of phase II.

## 1.3 Objectives of the paper

The global objective of this paper is to address the problem of optimizing the design of a phase II/phase III seamless study, and indirectly the dose selection, with the point of view of Decision Theory [14] and utility functions. The methodology can be formalized as follows:

- (i) Use Decision theory and utility functions to rationalize and optimize decision-making related to the choice of dose.
- (ii) Use this same framework to optimize the design of the phase II trial. This work is conducted in the context of adaptive seamless phase II/phase III trials: the aim is to identify the best timing for the interim analysis (ratio between the sample size at interim analysis and the total sample size) and the optimal allocation of patients within the doses arms at start of the study.

The beginning of Section 2 is devoted to the description of materials and methods, including all the required denotations, as well as the mathematical formalization of the efficacy dose-response modeling approach. We first proposed and discussed several types of utility functions and then we assessed, through simulations, their ability to identify an optimal design. Section 3 is dedicated to simulation results assessment and interpretations. Finally, Section 4 summarizes our decision-making framework, addressing the proposed method, and discussing the seamless design optimisation based on utility functions.

## 2 Materials and methods

The aim of this section is essentially to define the utility functions that attribute utility values to the sponsor's decisions, and then govern the choices: (decision to continue the trial after interim analyses, choice of dose). These utility functions can also be used to give guidance on an operationally seamless design, in terms of: timing of the interim analysis, design of the phase II part (stage 1). Several utility functions will be proposed and their properties will be discussed.

### 2.1 General notations and main notions

In this subsection, we describe the mathematical formalization of a phase II/phase III development program, aiming to define all necessary notations and calculations related to the dose-response modeling of efficacy, and to the PoS.

Here is the mathematical formalization of our modeling approach:

- (i) We consider one placebo  $d = 0$  and four active doses  $d = 2, 4, 6, 8$ .
- (ii)  $Y_{d,i}$  represents the random efficacy response of patient  $i$ , with  $i = 1, \dots, n_d$ , where  $n_d$  is the number of patients for the dose  $d$  in Phase II study. It is assumed that  $Y_{d,i} \sim N(m(d; \theta), \sigma^2)$  where  $m(d; \theta)$  is the expected mean effect of dose  $d$  and  $\sigma$  is the residual variability (standard deviation of residual error).
- (iii)  $N_2$  and  $N_3$  denote the phase II and III sample size respectively: in the context of a seamless design  $N_2 + N_3$  is a fixed constant,  $N_{tot}$ .
- (iv)  $w$  is a vector representative of the phase II design:  $w_d$  is the proportion of patients allocated to dose arm  $d$  ( $\sum_d w_d = 1$ ).
- (v) It is assumed that the expected mean dose-response for efficacy  $m(d; \theta)$ , follows an Emax model:

$$m(d; \theta) = \theta_1 + \frac{\theta_2 \times d}{\theta_3 + d}; \theta = (\theta_1, \theta_2, \theta_3)^t$$

- $\theta_1 = E_0$  is the placebo effect
- $\theta_2 = E_{max}$  is the maximum effect compared with placebo
- $\theta_3 = ED_{50}$  is the dose with half of the maximum effect

The Emax model will be used also by the sponsor as "working" model to estimate the mean dose-response relationship. Note that the choice of an Emax model was driven by the fact that it is the most frequently used model for efficacy in the literature, see [15];[16];[17];[18].

### 2.2 Utility functions: constructions and properties

In order to define and construct our utility functions, we consider the following assumptions:

- (i) The total sample size is fixed:  $N_{tot} = N_2 + N_3 = \text{constant}$ .
- (ii) The relative sample size of the phase II study with respect to the total sample size (phase II + phase III) is described with a parameter  $f$ ,  $0 \leq f \leq 1$ .
- (iii) The  $N_2 (= f \times N_{tot})$  patients are distributed in 4 doses and 1 placebo.

- (iv) The  $N_3 (= (1-f) \times N_{tot})$  patients are distributed in two arms: the selected dose and the placebo, each one with  $N_3/2$  patients.

The relative efficacy is denoted by  $\delta = \text{efficacy} / \text{maximum efficacy}$ , therefore we have:

$$\delta = \frac{E_{max} \times d / (ED_{50} + d)}{E_{max}} = d / (ED_{50} + d).$$

Therefore  $\delta$  varies between 0, for a null dose (placebo), and 1 for a very large (or “infinite”) dose.

In this subsection, we define utility functions that assign numerical values to the sponsor decisions at the end of the phase II part of the study. A typical example is the following utility function, that assign values to a combination of two decisions:

- Go/NoGo decision for entering phase III:
  - if ‘NoGo’  $\rightarrow$  cost of the phase II trial =  $-\gamma N_2$ ;
  - if ‘Go’ decision then the value depends on a random event, success or not of the phase III trial :  
if success of the phase III trial  $\rightarrow$  gain = Reward - total cost =  $R - \gamma N_{tot}$
- if ‘Go’ decision then the sponsor must choose the adequate dose within the doses tested in the phase II study.

The utility value is in fact random after the phase II stage, as the final reward depends on the success, or not, of the phase III part. Therefore, from the sponsor’s point of view, the expectation of final utility value is the key quantity to assess; it depends on the expectation of reward after the phase III and, as a consequence, depends on the Probability of Success of the phase III part, that we call PoS, in the following. For further computational details regarding the PoS, see Appendix A.1.

It should be noted that for this utility function, named  $U0$  in the following, we have defined ‘Success’ in phase III by simultaneously a statistically significant comparison with the control in the phase III trial and the absence of safety issues in the same phase III trial: the probability of absence of safety issues is modeled as a function of dose,  $d$ ,  $1 - sa \times (d/d_K)^2$ , where  $d_K$  is the highest dose in the design and  $sa$  is a parameter corresponding to the probability of safety concern with the highest dose of the design. In this case, the PoS is the product of the PoS for efficacy by the probability of absence of safety issue. This utility function has been proposed in [19]. Such a utility function has appealing properties, in particular the easy interpretation of the parameters. But the problem with such utility functions is that some of the parameters (in particular,  $R$ , the financial reward if the program is successful, and  $sa$ , the safety parameter, which is fixed also) are not known with enough confidence or precision at the beginning of the drug clinical development.

More generally, a proper utility function should have the following properties:

- (i) It must depend on success of the phase III study (higher utility in case of success)
- (ii) It must not be a non-monotonic concave function of the dose with a unique maximum value (increasing then decreasing): such a shape reflects the bi-dimensional aspect of the utility function: one increasing with the dose (efficacy component) the other one decreasing with the dose (safety component)

Examples of utility functions verifying those conditions are shown below, and some are plotted in Figure 1:

1.  $U0(d, f) = -\gamma N_2 \mathbb{1}(NoGo) + \mathbb{1}(Go)(-\gamma N_{tot} + R \times PoS_{adj}(d))$
2.  $U1(d, f) = -\gamma N_{tot} + PoS(d) \times (R - c(\delta - 0.95)^2)$

3.  $U2(d, f) = -\gamma N_{tot} + PoS(d) \times R_{max}(1 - \delta)$
4.  $U3(d, f) = -\gamma N_{tot} + PoS(d) \times R_{max}(1 - \delta)^2$
5.  $U4(d, f) = PoS(d) \times (1 - c(\delta - 0.95)^2)$
6.  $U5(d, f) = PoS(d) \times (1 - c \times \delta)$
7.  $U6(d, f) = PoS(d) \times (1 - c \times \delta)^2$
8.  $U7(d, f) = -\gamma N_{tot} + PoS(d) \times (R - c(\delta - 0.95)^2 \mathbb{1}(\delta > 0.95))$
9.  $U8(d, f) = PoS(d) \times (1 - c(\delta - 0.95)^2 \mathbb{1}(\delta > 0.95))$
10.  $U9(d, f) = PoS(d) \times (1 - c \times (d_k/d_{max})^2)$  (where  $d_k$  is the dose and  $d_{max}$  is the highest dose)
11.  $U10(d, f) = PoS(d) \times (1 - PoT(d))^k$  (where  $PoT(d)$  is the probability of toxicity for dose  $d$ )
12.  $U11(d, f) = PoS(d)^h \times P(tox_{obs}(d) \leq 0.15)^k$

The  $PoS_{adj}$  component denotes the adjusted efficacy PoS (i.e. 'Success', defined by both simultaneously a statistically significant comparison with the control in the phase III trial (efficacy PoS) and the absence of safety issues in the same phase III trial):  $PoS_{adj}(d) = PoS(d) \times (1 - sa(d/d_k)^2)$ .

The  $P(tox_{obs}(d) \leq 0.15)^k$  component is defined as follows: the number of patients having a critical toxicity is a binomial distribution of parameters  $N_3/2$  and  $\pi(d)$ , where  $\pi(d)$  is the probability of toxicity for dose  $d$ ; the quantity  $tox_{obs}$  is the observed proportion of patients having a critical toxicity in phase III,  $tox_{obs} = \#patients \text{ with critical toxicity} / (N_3/2)$ ; so  $P(tox_{obs}(d) \leq 0.15)$  is then the predictive probability of controlling over-toxicity, i.e. the predictive probability of observing a toxicity rate 0.15 in phase III. Note that 0.15 is an arbitrary choice in this paper, but this choice usually depends on the therapeutic area. For instance, a threshold of 0.30 (or 0.40) is more common in oncology and may vary in other areas.

For both  $PoT(d)$  and  $P(tox_{obs}(d) \leq 0.15)$  safety components, we used the following Probit model:  $\pi(d) = P(W = 1|d) = \Phi(\lambda_1 + \lambda_2 \times d)$ ,  $\lambda = (\lambda_1, \lambda_2)^t$ , where  $\lambda_1 = a$  is the intercept parameter,  $\lambda_2 = b$  is the dose effect,  $W$  is the global toxicity profile for one patient, captured by a binary outcome, 1 for critical toxicity and 0 if no critical toxicity, and  $\Phi$  is the Cumulative Distribution Function (CDF) of the standard normal distribution.

Parameters  $h$  and  $k$  reflect the respective contributions of efficacy safety to the utility function; for instance, the higher the  $k$ , the higher the penalty for safety.

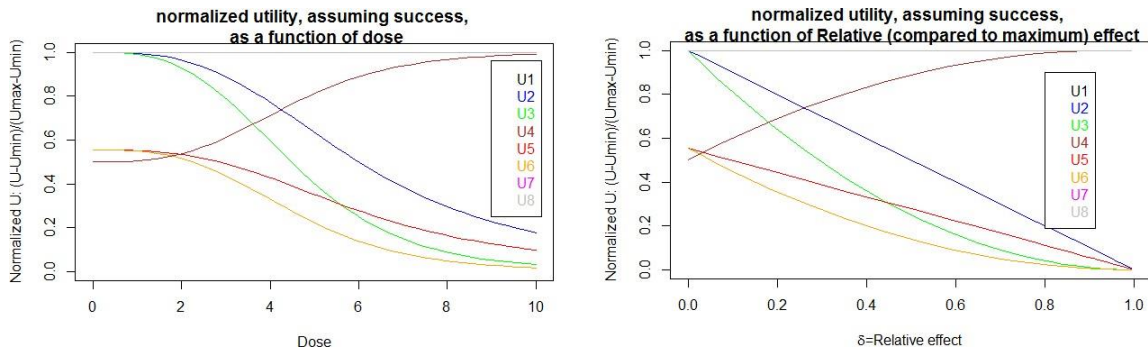


Figure 1: Overview of some utility functions

The utility functions  $U1$  to  $U9$  do not explicitly refer to the efficacy and safety components but have the desired concavity property. In the utility functions  $U1$  to  $U8$ , in order to normalize the effect of the dose (so

that it does not depend on the dose unit), the effect is expressed as a function of  $\delta$ : the main problem with such a definition is that, for the sponsor’s point of view, the utility function depends also on the estimation of the efficacy dose-response model; on the contrary, the  $U9$  utility function does not depend on the efficacy dose-response model. On the contrary the utility functions  $U10$  and  $U11$  explicitly identify both an efficacy and a safety component.

## 2.3 Seamless design and utility function

The aim of this subsection is to give guidance on an operationally seamless design, in terms of: timing of the interim analysis, design of the phase II part (stage 1). The main underlying hypothesis is that the sponsor takes its decisions (decision to continue the trial after interim analyses, choice of dose) in maximizing a utility function that assigns a value to each decision. To do that, some of the utility functions defined in the previous section will be discussed according to their relative simulation results.

### 2.3.1 Introduction and notations

Before study starts: sponsor’s general strategy is to maximize (in phase II design,  $w$ , and  $N_2/N_{tot}$  ratio,  $f$ ) the expected utility. A frequentist approach was used to compute the parameters estimates of dose-response model: sponsor’s decisions are driven by maximum likelihood estimations of the model parameters. Decision rule of the sponsor is only based on point estimate of model parameter  $\hat{\theta}$ . We compared the properties of the decision rules through clinical trial simulations, corresponding results are shown in Section 3. The simulations were not conducted in simulating individual patients but in simulating directly the maximum likelihood parameter estimates by sampling them with a Normal distribution  $N(\theta; I_{\theta}^{-1})$ , where  $I$  is the Fisher information matrix.

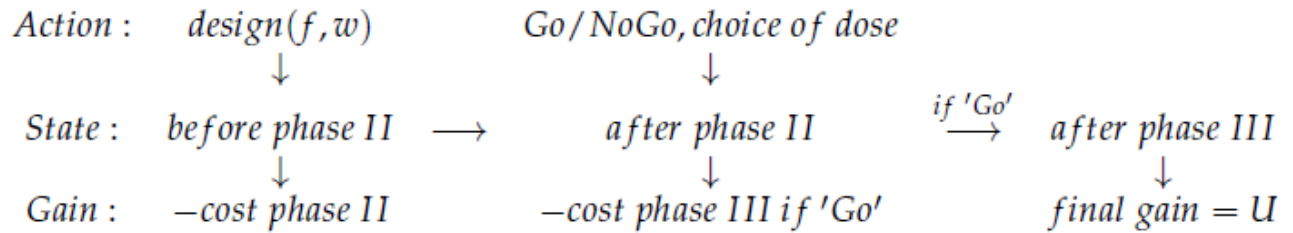
### 2.3.2 Optimal patient allocation

All utility functions presented in Section 2.2 were assessed through several simulation scenarios, but for sake of simplicity, only some particular functions of interest are presented in this paper. Regarding the optimisation of patient allocation to doses as well as the global patient allocation between phase II and phase III, we compared in this paper, through simulations, results obtained in using respectively the utility functions  $U5$  and  $U9$  only (additional results for  $U2$  are given in Appendix A.2).

For the purpose of explicit safety modeling (via a dose-response function), utility functions of the form  $U10$  or  $U11$  are the most appropriate. But, what is striking about the utility function  $U10$  is that efficacy and toxicity are not perfectly treated at the same level. Indeed, the efficacy component,  $PoS(d)$ , involves both the effect size of the dose  $d$  and the sample size of the phase III study whereas in comparison, the toxicity component,  $(1 - PoT(d))^k$ , only involves the toxicity level of the dose  $d$  without involving the sample size of the phase III study at all. This asymmetry is troublesome when it comes to optimizing the allocation of patients between phase II and phase III, and for this reason,  $U11$  was proposed. A specific characteristic of  $U11$  is that both its efficacy and safety components depend on the sample size of the phase III study. This choice is intended to reflect real life conditions where Go/NoGo decisions and dose selection at the end of phase II always relate to the sample size the sponsor can afford for phase III. This can be viewed as a pragmatic choice. Results obtained in using  $U10$  and  $U11$  are not given in this paper.

## 2.4 Sponsor’s strategy: Optimal dose and decision rules

Our utility-based decision framework can be described in the context of a Markov Decision Process [20]. In particular, the most comprehensive decision framework in our context, the one corresponding to the utility  $U0$ , can be described by the following graph.



According to this graph:

- (i) At start of the study the sponsor can act on the design of the trial: the timing of the interim analysis (the ratio,  $f$ , of the phase II sample size by the total sample size) and the allocation of the phase II patients to the dose arms (vector  $w$ ). This action has a cost which is proportional to sample size in phase II:  $\gamma N_2$ .
- (ii) When the phase II part is completed, the sponsor analyzes the data and takes 2 decisions: decides to go the phase III or not and, in case of positive answer, chooses the dose for the phase III.
- (iii) When the phase III is completed: if it is successful then there is a reward,  $R$ , and the final gain is  $U = R - \gamma N_2 - \gamma N_3 = R - \gamma N_{tot}$ ; if it not successful then there is total cost, and the utility is negative  $\rightarrow U = -\gamma N_{tot}$

In an uncertain environment like this one, the sponsor's strategy (the set of actions) is to optimize the mean utility  $E(U)$ . According to the Bellman Dynamic Programming principle, this optimisation should be performed backwards:

1. given the phase II trial has been performed the, the optimal decisions (Go/NoGo, choice of dose) maximize  $E_{dose=d}(U) \rightarrow U_*(f, w) = \max_d E_{dose=d}(U)$ ; at this stage only the reward,  $R$ , is random: it depends on the success or not of the phase III trial; therefore:  $U_*(f, w) = \max_d E_{dose=d}(R) - \gamma N_{tot}$ ; this quantity  $E(R)$  depends on the adjusted PoS, which plays a key role in the calculations
2. the sponsor chooses 'Go' if  $PoS_{adj}$  associated to the best dose  $d^*$  is  $\geq 0.30$  &  $U_*(f, w) = \max_d E_{dose=d}(U) > 0 \Leftrightarrow PoS_{adj}(d^*) \geq 0.30$  &  $\max_d E_{dose=d}(R) > \gamma N_{tot}$ , otherwise the sponsor should choose 'NoGo'
3. the optimal design maximizes  $EU_*(f, w)$

For the utility functions  $U1, \dots, U11$  the decision process has been slightly simplified: because for those utilities there is no reference to economics costs, we have proposed to base the decision to go to phase III or not on a minimal value of the PoS only, that we have also set to 0.30: the sponsor decides to go in to phase III if the estimated PoS associated to the best dose is  $\geq 0.30$ .

In the following we detail the methodology related to the points 1. and 3.

### 2.4.1 The computation of PoS

The efficacy PoS computed by the sponsor, for dose selection, uses the point estimate  $\hat{\theta}$  of  $\theta$ .

In the method shown in Appendix A.1, the sponsor uses the raw value of the estimate of the model parameters to estimate the PoS as if it was the true parameter value. In a more conservative approach, the sponsor might want to consider the uncertainty in the parameter value: in that case a hierarchical approach can be used.

The hierarchical model approach is as follows:

- Given  $\theta, \bar{\Delta}(d) | phase\ II \sim N(m(d; \theta), 2SE^2)$  since  $m(0; \theta) = 0$  (because  $E_0 = 0$  in our chosen scenarios) and approximately,  $\theta \sim N(\hat{\theta}, I_{\hat{\theta}}^{-1})$ ; then by linearization (delta-method):

$m(d; \theta) \simeq m(d; \hat{\theta}) + \nabla m(d; \hat{\theta})^t \cdot (\theta - \hat{\theta})$ , where  $\nabla$  is the gradient

$$\Rightarrow m(d; \theta) \sim N(m(d; \hat{\theta}), \nabla m(d; \hat{\theta})^t I_{\hat{\theta}}^{-1} \nabla m(d; \hat{\theta}))$$

$$\Rightarrow \bar{\Delta}(d) | \text{phase II} \sim N(m(d; \hat{\theta}), 2SE^2 + \nabla m(d; \hat{\theta})^t I_{\hat{\theta}}^{-1} \nabla m(d; \hat{\theta}))$$

$$\widehat{PoS}(d) = \Phi \left( \frac{m(d; \hat{\theta}) - 1.96 \times \sqrt{2SE^2}}{\sqrt{2SE^2 + \nabla m(d; \hat{\theta})^t I_{\hat{\theta}}^{-1} \nabla m(d; \hat{\theta})}} \right)$$

**Accounting for uncertainty induces decrease of the estimated PoS, consequently, sponsor is encouraged to increase the dose to compensate**

- With this approach, issues arise when  $I_{\hat{\theta}}$  is singular. A possible solution would be as follows.

When computing  $\frac{1}{N_{sim}} \sum_{r=1}^{N_{sim}} U(\hat{\theta}_r)$ , keep only those for which  $I_{\hat{\theta}}$  is nonsingular:

\* drawback: increases computation time

\* one needs to check, using the PoS that does not account for uncertainty, that

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

does not change too much when only replicates with nonsingular  $I_{\hat{\theta}}$  are kept

We essentially considered the case in which the sponsor only uses the estimate of the parameter to compute the PoS.

## 2.4.2 Optimizing the design

Regarding  $U_0$ , the expectation is computed via numerical integration:  $E(U) = \int \left( (-\gamma \times f N_{tot}) \times (1 - Go(\theta)) + (-\gamma \times N_{tot} + R \times PoS_{adj}(\theta_0)(d(\theta))) \times Go(\theta) \right) p(\theta) d\theta$ , where  $p(\theta)$  is the density of a Gaussian distribution centered at the true value of the parameters and with covariance matrix equal to the inverse of the Fisher matrix.

For  $U_1, \dots, U_{11}$ , the expectation is computed via simulation. In fact,  $E(U(d^*) | \text{phase II})$  is a function,  $U$ , of  $\hat{\theta} \Rightarrow E_{w,f}^{(\text{phase II})} E(U(d^*) | \text{phase II}) = E^{(\hat{\theta})} U(\hat{\theta})$ , with  $\hat{\theta} \sim N(\theta, I_{\theta}^{-1})$ .

Then  $E_{w,f}^{(\text{phase II})} E(U(d^*) | \text{phase II})$  can be estimated by:  $\frac{1}{N_{sim}} \sum_{r=1}^{N_{sim}} U(\hat{\theta}_r)$ , where the  $\hat{\theta}_r$  are sampled from  $N(\theta, I_{\theta}^{-1})$ .

The strategy is as follows:

- (i) After phase II, for a given utility  $U(d, f)$ :

- compute  $E(U(d, f) | \text{phase II})$  for each dose  $d$
- compute  $d^* = \arg \max_d E(U(d, f) | \text{phase II})$
- for  $U_1, \dots, U_{11}$  (except for  $U_0$ , see discussion above), decide if worth going to phase III if:

$$PoS(d^*) \geq 0.30$$

- (ii) Before phase II:

The sponsor's strategy before the phase II consists in optimizing the timing of the interim analysis (the ratio,  $f$ , of the phase II sample size divided by the total sample size) as well as the allocation of the phase II patients to the dose arms (vector  $w$ ). Mathematically this can be written as:  $(w^*, f^*) = \arg \max_{w,f} E_{w,f}^{(\text{phase II})} E(U(d^*) | \text{phase II})$ . In practice:



- $E_{w,f}^{(phaseII)} E(U(d^*) | phase II)$  is computed via numerical integration or estimated through simulations, as explained above
- The optimisation was conducted using Nelder-Mead algorithm (after logistic transforms to ensure that  $0 < f < 1$  and  $\sum_d w_d = 1$ ) with the R 'optim' function.
- This optimisation could be conducted either separately (optimize  $f$  while  $w$  is fixed, or  $w$  while  $f$  is fixed) or simultaneously (optimize  $f$  and  $w$  at the same time)

## 2.5 Simulation protocol and scenarios

The maximum effect size simulated in the example is 0.4. We consider the following fixed total sample size,  $N_{tot} = 2000$ . The residual variability is assumed to be known and set to the value of 1 in the simulations. This value has been chosen in order to have, for one of our most important scenarios, named "Sigmoid" (defined below), an effect size (the ratio of the expected difference versus placebo divided by the common standard deviation) of 0.4 for the highest dose ( $d=8$ ) of our design. This effect size is in the range/order of magnitude of effect size generally targeted in drug development (it is admitted that the standard effect size of clinical importance observed from most clinical trials is within the range of 0.25 and 0.5, see [21]). According to simulation results,  $\sigma = 1$  seemed to be a reasonable choice in terms of estimation quality and dose choice. Regarding  $U0$ , costs/Reward parameter values are set to the same values as in J.Temple thesis[19]:  $R=reward=12000$  and  $\gamma=cost\ per\ patient=1$ . In  $U0$ , the function for safety assumes that the maximum probability of phase III failing due to safety is  $sa$ , several values of  $sa$  is assessed,  $sa = 0.01, 0.05, 0.10, 0.20$  and  $0.50$ .

The ' $c$ ' coefficient is set to 0.8 in all utility functions depending on it: it was calibrated so that the highest tested dose is located after the peak of the utility curve, this exemplifies the model's behavior, and shows that it does not necessarily select the highest dose all the time.

The mean utility is computed via simulations,  $N_{sim} = 10000$   $\hat{\theta}$  replicates are generated. Tables summarizing simulation results of the 10000 simulated studies are presented in Section 3, each result is an average value calculated over all phase II studies.

We consider in this paper two main efficacy scenarios assumed to be the true ones reflecting the real dose-response:

- (i) Sigmoid scenario: this scenario is monotonic, that is, the mean response is strictly increasing as a function of the dose; for this scenario, the true efficacy model parameters values are:  $(E_{max}, ED_{50}, E_0)=(0.22, 6, 0)$ .
- (ii) Plateau scenario: this scenario begins with an almost linear growth, followed by an inflection, and then stabilizes at the end, which means that the last two doses have the same efficacy; for this scenario, the true efficacy model parameters values are:  $(E_{max}, ED_{50}, E_0)=(0.14, 0.9, 0)$ .

## 3 Results

The aim of this section is the following:

1. illustrate influence of safety (as the dose grows) on the PoS of the utility  $U0$ , as well as the impact of both safety and relative sample size (with respect to total sample size) on the expected utility  $E(U0)$
2. illustrate how utilities  $U5$  and  $U9$  can be used to optimize the seamless phase II/phase III design study

### 3.1 Results for $U0$

In the following, the aim is to graphically examine the impact of safety on the PoS. Figure 2 shows the PoS by dose for various values of the safety parameter and for 600 patients in phase III.

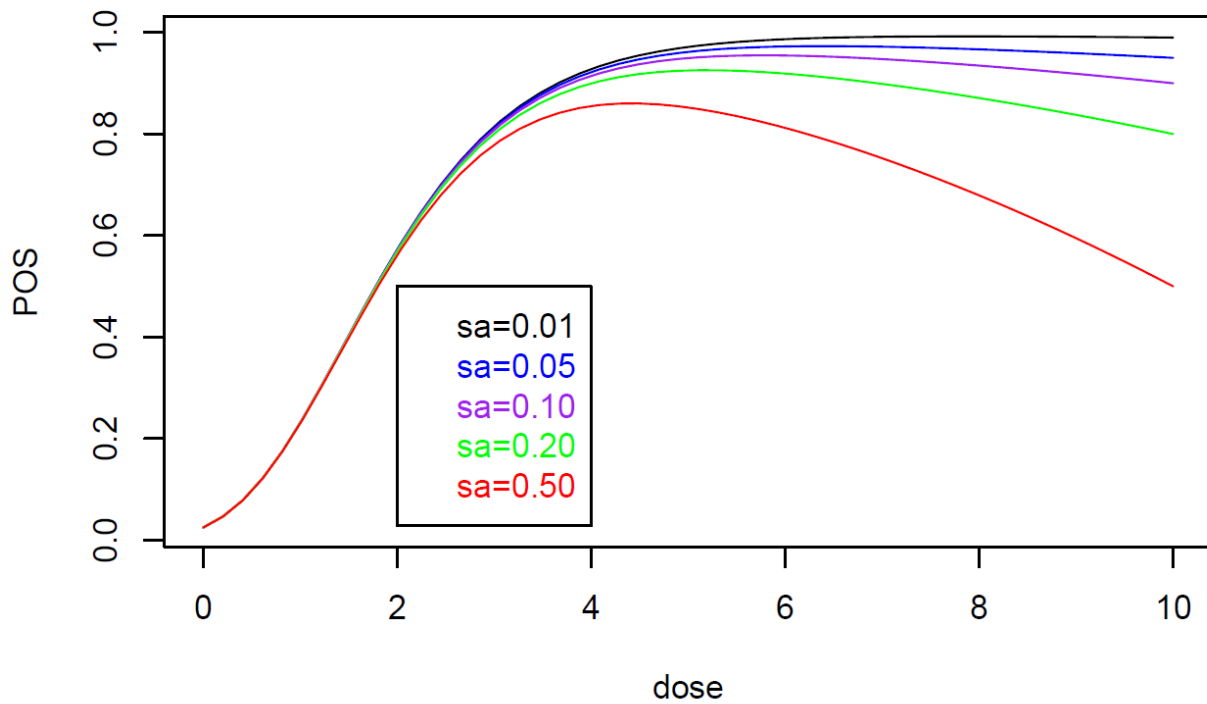


Figure 2: PoS by dose for various values of the safety parameter

Concerning the computation of mean utility, two methods of integration were used:

- One based on a quadrature method for multidimensional integrals (cubature package)
- The other one based on successive calls of the R "integrate" function

The first method seems to be the fastest. A possible theme or research for further development could be to use Laplace approximation method to compute the integrals when optimizing.

In the following, we plotted  $E(U)$  graphs as a function of  $N_2$ , for several scenarios (where scenarios refer here to Sigmoid efficacy profile and several values of 'sa'). These graphs are represented for a balanced design.

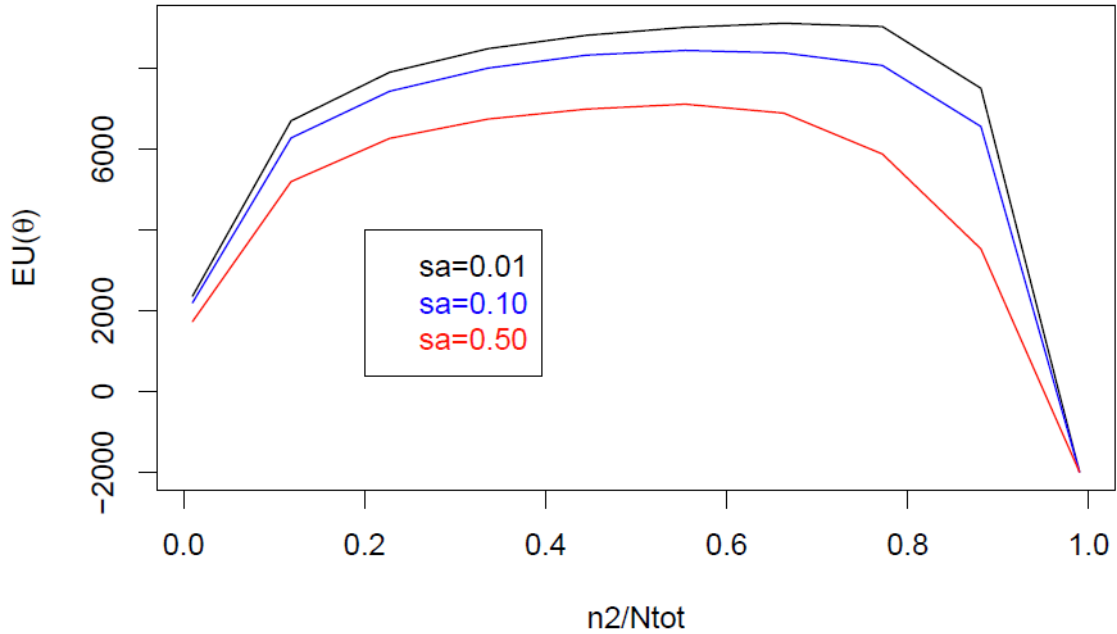


Figure 3: Utility as a function of phase II sample size and safety  $sa$

In Figure 3:

- Utility increases when safety is better
- With this dose-response function: the phase II needs to be larger than phase III
- The worse the safety, the larger needs to be the phase III (because the sponsor selects a lower dose)

### Conclusion

From these analyses we noticed that, at least for balanced design, the optimal sample size of the phase II part of the seamless design can be quite large.

In the following, we will tackle the problem of the optimisation of the design (optimal repartition of the patients between treatment arms) of the phase II part, in addition to the problem of optimisation of its total sample size. For this purpose, as we noticed that the computation time of the expectations  $E(U)$  with numerical integration routines were very long, we will, for these next parts, rather use simulations.

### 3.2 Optimisation of the seamless design based on U5 and U9 utility functions

It is recalled that  $U5$  and  $U9$  are defined as follows:

$$U5(d, f) = PoS(d) \times (1 - c \times \delta)$$

$$U9(d, f) = PoS(d) \times (1 - c \times (d_k/d_{max})^2)$$

In the following, a graph highlighting the theoretical curves related to the Sigmoid scenario is drawn for each utility function, where the blue curve is the PoS, the dotted curve is the penalty and the black curve is the utility, i.e. the product of  $PoS \times$  penalty, and a table summarizing all the simulation results is given. This table contains the following:  $w$  is the design (patients allocation per dose),  $f$  is the parameter representing the distribution between phase II and phase III, 'Go' is the probability of going to phase III with the chosen dose, 'doses' represents probabilities of choosing  $d = 2$ ,  $d = 4$ ,  $d = 6$  and  $d = 8$  respectively among

the 'Go', POS(go) is the POSs mean among the 'Go' with the chosen dose and E(U) is the expected utility of the chosen dose for the 10000 simulated phase II studies among 'Go' and 'NoGo' decisions (utility is set to 0 when it is a 'NoGo' decision).

Optimisations of patient allocation to doses and global allocation ratio between phase II and phase III are conducted separately (for  $U5$ ,  $w$  is optimized while  $f$  is fixed, and for  $U9$ ,  $f$  is optimized while  $w$  is fixed).

### 3.2.1 Results for U5

Figure 4 is a plot containing the three theoretical curves related to  $U5$ .

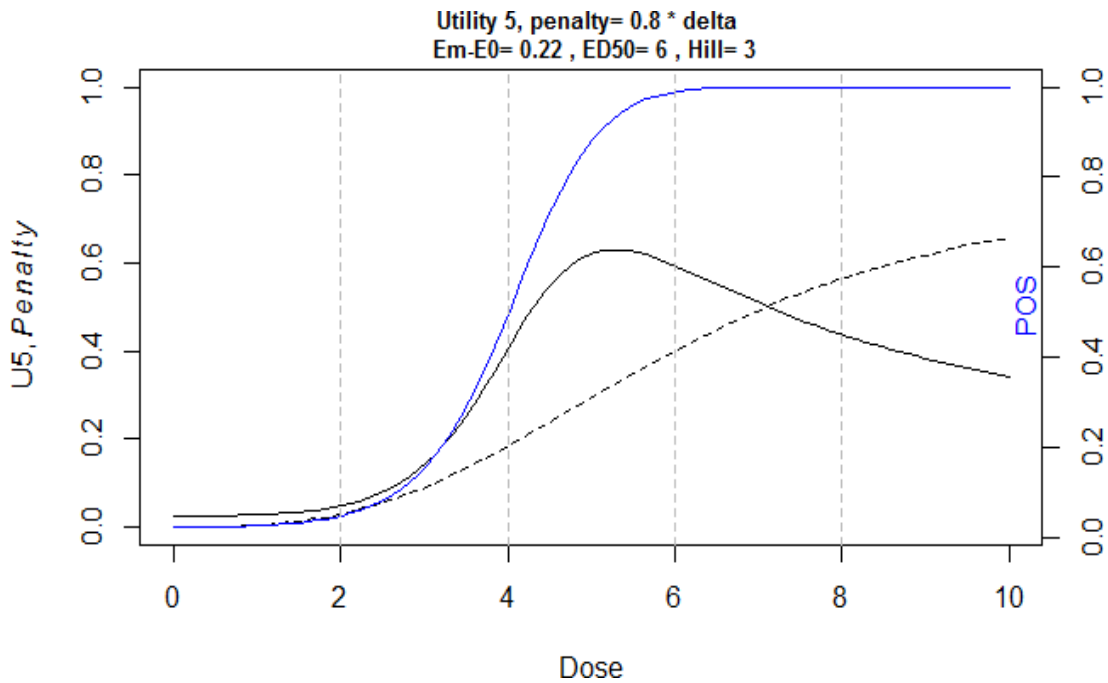


Figure 4: Theoretical curves for U5, Sigmoid scenario

Results related to the balanced design (i.e. patients are equally allocated to doses), are given in Table 1.

## Non optimal

sigmoid	plateau
$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ , $f = 0.25$	$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ , $f = 0.25$
Go=:63%	Go=:94%
doses= 0.47, 0.21, 0.19, 0.14	doses= 0.66, 0.21, 0.04, 0.09
POS(go)=45%	POS(go)=90%
E(U)= 0.16	E(U)= 0.40

Table 1: Balanced design -patients are equally allocated to doses- for  $U_5$ , Sigmoid and Plateau scenarios

By comparing results to the theoretical utility graph, we can see that  $d = 2$  is recommended with a very high probability:  $d = 2$  is chosen in 47% of cases if 'Go', in Sigmoid scenario.

The optimal design results ( $w^*$ ) for both Sigmoid and Plateau scenarios, with  $f = 0.25$ , are given in Table 2.

## Optimal design

sigmoid	Plateau
$w = (0.21, 0.21, 0.21, 0.19, 0.18)$ , $f = 0.25$	$w = (0.22, 0.18, 0.19, 0.21, 0.20)$ , $f = 0.25$
Go=:63%	Go=:94%
doses= 0.46, 0.22, 0.18, 0.14	doses= 0.65, 0.21, 0.05, 0.09
POS(go)=45%	POS(go)=90%
E(U)= 0.16	E(U)= 0.39

Table 2: Optimal design -optimizing the dose allocation ratio- for  $U_5$ , Sigmoid and Plateau scenarios, with  $f = 0.25$

The balanced design is almost the optimal design. In addition, there is no real gain brought by the optimisation compared to the balanced design, the probabilities of 'Go', the choice of doses, the POSs mean and the expectations of utility are almost the same (for the Plateau scenario for example, design optimisation decreases the average utility by 0.01% compared to the balanced design).

Moreover, we can see that recommended doses do not seem to be consistent with Sigmoid and Plateau scenarios:  $d = 2$  is too much recommended, whereas the best two doses  $d = 4$  and  $d = 6$  according to the theoretical utility. Note that for the Plateau scenario, the optimal design performs slightly better in selecting less often the one of the first two doses, in addition, design optimisation does not increase the average utility compared to the balanced design; in such a favorable scenario -Plateau- there is little/less room for improvement anyway compared to the Sigmoid scenario. There was no noticed gain either for the Sigmoid scenario: design optimisation does not increase the average utility compared to the balanced design, it remains almost the same for both designs (optimal and balanced designs). Bad dose choices are due to the fact that phase II sample size is too small (500 patients) for this sigmoid model which leads to often bad estimations and consequently, bad decisions.

One can try to show that if phase II was larger, the decisions would be better and the global expectation of

U5 would be closer to the theoretical curve previously shown. To do so, we investigated two approaches described in the following.

### First approach, increase the $f$

Indeed, it is possible to increase the phase II by increasing the  $f$ , but by increasing  $f$ , we decrease phase III: so if we increase the  $f$ , we cannot compare ourselves to this curve above because it is based on theoretical PoS for a phase III of 1500 patients. Nevertheless, we can verify that if  $f$  increases, the probability of choosing  $d = 2$  will decrease, but the utility will eventually decrease also by lack of patients in phase III (see Table 3).

<b>sigmoid</b>
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)= 0.16
<b>sigmoid</b>
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)= 0.22
<b>sigmoid</b>
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)= 0.22
<b>sigmoid</b>
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)= 0.06

Table 3: Simulation results for U5 with the balanced design (patients are equally allocated to doses), Sigmoid scenario, by increasing  $f$

Based on Table 3, we can clearly see that by increasing the sample size of phase II, we reduce the probability of choosing  $d = 2$  (but we also make bad choices because the more  $f$  increases, the more we choose the highest dose: we compensate the loss of the number of Patients in phase III by the selection of the most effective dose).

### Second approach

We examined obtained results when we increase the phase II, by considering  $N_2 = 2000$  patients, and by fixing phase III sample size,  $N_3 = 1500$  patients.

With  $N_2 = 2000$  patients, we obtain:

- Prob(choosing  $d = 2$ ) = 17%
- Prob(choosing  $d = 4$ ) = 36%
- Prob(choosing  $d = 6$ ) = 41%
- Prob(choosing  $d = 8$ ) = 9%

This time better decisions are made:  $d = 2$  is rarely chosen (17% of cases), but  $d = 4$  or  $d = 6$  are very often chosen (one or the other is chosen in 77% of the cases, optimal dose being  $d = 6$  according to theory).

It is very important to note that the "theoretical" utility depends on the size of the phase III, and therefore, the optimal dose depends on the size of the phase III: optimal dose increases when  $f$  increases: since  $N_{tot}$  is constant, when  $N_2$  increases,  $N_3$  decreases which induces that higher doses are necessary to have a sufficiently high PoS, see Figure 5.

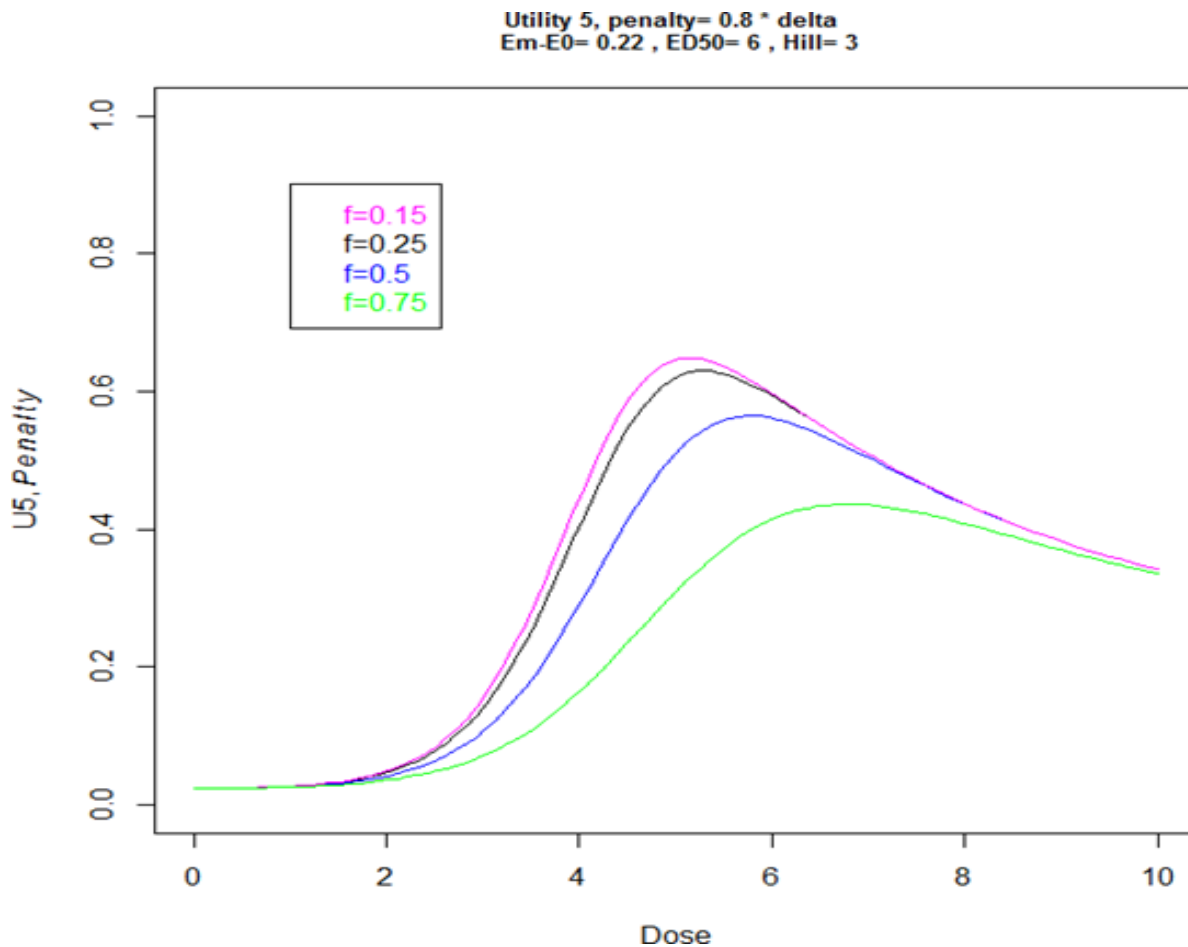


Figure 5: Theoretical utilities as a function of the dose and  $f$

### Modification of optimisation strategy

In the following subsection, we have decided to work on a global patient allocation between phase II and phase III optimization only, with a balanced design, for the following utility function:

$$U9(d, f) = PoS(d) \times (1 - c \times (d_k/d_{max})^2).$$

In fact, according to all previous results, there was no difference between the optimal and balanced designs when it comes to patients allocation to doses, and no real gain was noticed regarding the PoS, the global

utility and the 'Go' proportion in phase III. So now, we will only work with a balanced  $w$  design, but this time we will seek to optimize the patients between phase II and phase III, that is to say, we will proceed an overall optimisation of the patients allocation between phase II and phase III (while maintaining a fixed total number as before,  $N_2 + N_3 = 2000$ ).

In the following, we also included a second constraint in the decision rule: the PoS must be  $> 0.30$  and the effect difference between placebo and the recommended dose must be  $> 0.04$  (to eliminate low doses). In fact, the threshold here (0.04) was chosen on the basis of the theoretical effect of  $d = 2$  (i.e. the lowest dose) obtained with the three-parameter Emax model ( $E_0$ ,  $E_{max}$  and  $ED_{50}$ ), which is 0.055. In general, these thresholds are pre-clinically defined, but here, for our simulations, we considered a threshold equal to 0.04.

### 3.2.2 Results for U9

The theoretical utility, PoS and penalty curves for  $U_9$  are shown in Figure 6 below.

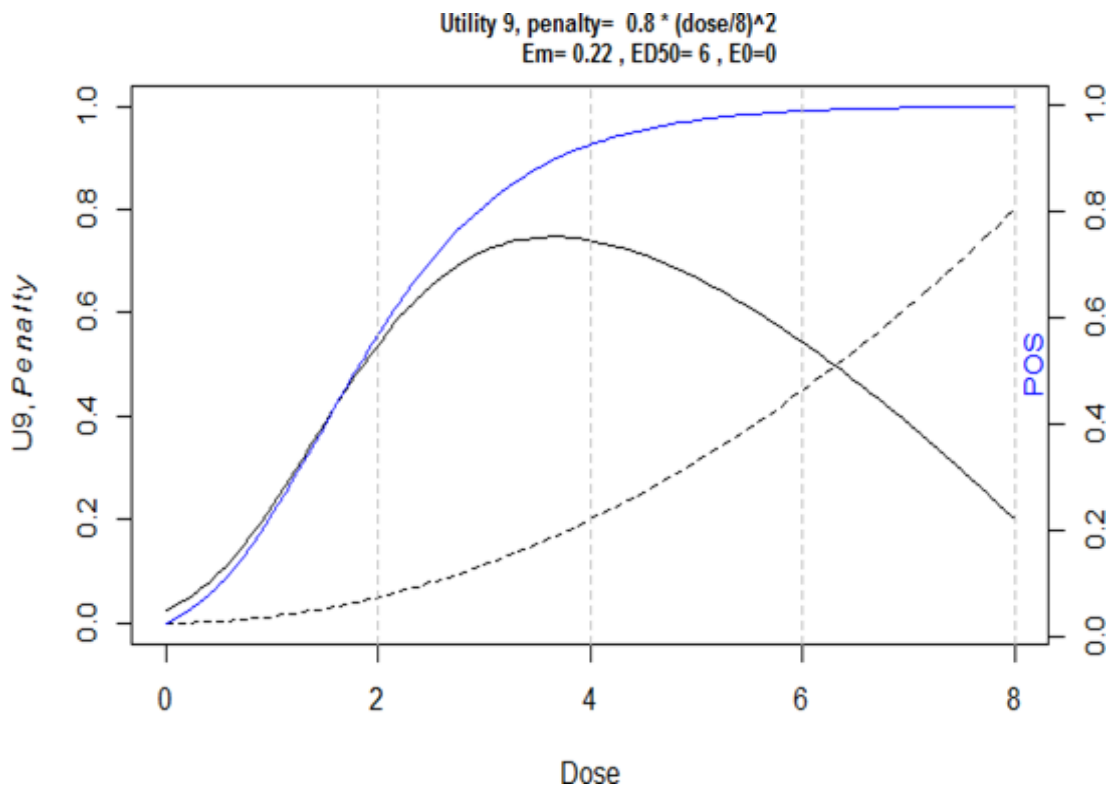


Figure 6: Theoretical curves for  $U_9$ , Sigmoid scenario

The comparisons of the Sigmoid and Plateau scenarios, between the non-optimal design (i.e. fixed  $f$  between phase II and phase III, we compared different fixed values of  $f$ ), and the optimal design (optimizing the patients allocation between phase II and phase III) are given in Table 4.

We recall that we are working here with a balanced design, i.e.  $w$  is fixed and the objective is to optimize  $f$  only.



## Non optimal

	sigmoid	plateau
<b>f=0.10</b>	$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ Go=51% doses= 0.44, 0.32, 0.17, 0.07 POS(go)=83% E(U)= 0.31	$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ Go=66% doses=0.74, 0.16, 0.07, 0.03 POS(go)=99% E(U)= 0.56
<b>f=0.25</b>	$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ Go=74% doses= 0.32, 0.41, 0.21, 0.06 POS(go)=83% E(U)= 0.44	$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ Go=86% doses= 0.69, 0.21, 0.08, 0.03 POS(go)=97% E(U)= 0.72
<b>f=0.50</b>	$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ Go=86% doses= 0.17, 0.52, 0.25, 0.05 POS(go)=77% E(U)= 0.46	$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ Go=94% doses= 0.61, 0.29, 0.08, 0.02 POS(go)=90% E(U)= 0.71

## Optimal

sigmoid	plateau
$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ , <b>f=0.40</b> Go=83% doses= 0.23, 0.49, 0.23, 0.05 POS(go)=80% E(U)= 0.47	$w = (0.2, 0.2, 0.2, 0.2, 0.2)$ , <b>f=0.37</b> Go=92% doses=0.65, 0.25, 0.08, 0.02 POS(go)=95% E(U)=0.74

Table 4: Optimal versus non-optimal design for  $U_9$ , where optimal design consists here in optimizing the global patient allocation between phase II and phase III, Sigmoid and Plateau scenarios

Based on Table 4, parameters are well estimated and correct decisions and dose choices are made.

On the other hand, according to the optimal design above, it is recommended to increase the number of patients in phase II to make a better choice, which amounts to the idea that we tried to prove previously with  $U_5$ , by increasing the sample size of phase II.

Additional results regarding  $U_9$  are given in Appendix A.3: utility expectations (after the sponsor's choice: Go and dose choice) are plotted as a function of  $f$ , for both Sigmoid and Plateau scenarios.

## 1.1 Concluding remarks

We have proposed a general decision-making framework, suitable for comparing and optimizing seamless phase II/ phase III designs, based on utility functions. We have reviewed and discussed various forms of utility functions, that either appeared reasonable for us or were previously mentioned in the literature. Because we think that utility functions defined by economic or financial considerations (such as the cost of phase III, expected financial reward in case of successful launch of the drug) are difficult to specify with enough confidence or precision at the beginning of the drug clinical development, we preferred to focus on utility functions only defined by efficacy and safety (explicitly or implicitly) considerations. We performed then a simulation study with those utility functions that appeared the most appropriate to us, in particular the  $U_5$  and  $U_9$  utility functions. Unfortunately, the results obtained were not fully satisfactory, as no real gain was noticed when optimizing patient's allocation to doses: the optimal designs identified were, in most cases, very close to the standard balanced design. So, optimizing the dose allocation ratio in

stage 2 of the dose-finding study offered very little improvement in regard to significantly increased operational complexity and consequently, this optimisation part becomes debatable, and needs to be properly improved/refined.

## 2 Discussion and Conclusions

In the context of seamless phase II/phase III study design, we have defined a Statistical Decision framework in which the sponsor needs to take sequential decisions with the objective of maximizing the expected future utility. For this matter, we proposed and discussed various forms of utility functions: for all of them, the calculation of their expectations involved the calculation of the Probability of Success in phase III. In terms of statistical methodology, we considered there a frequentist approach: the sponsor analyzes the data of the intermediate analysis (the phase II part of the seamless design) using a parametric model of the Emax type via maximum likelihood estimation but we considered the possibility that the sponsor takes into account the uncertainty regarding his estimation of the dose-response function to take these decisions. We expected this framework to enable comparisons of different seamless designs, a design being defined by the ratio between the sample size at the interim analysis and the total sample size and also by the distribution of patients among the dose groups at the beginning of phase II. For this purpose, we performed trial simulations with the objectives of identifying the optimal seamless designs, for some of the most relevant utility functions discussed, but this exercise was not fully successful: the optimal designs identified were, in most cases, very close to the standard balanced design. But this work has also highlighted the crucial importance of the size of phase II with, for some scenarios, an optimal allocation allocating more patients in phase II than in phase III (see results for  $U_2$  in Appendix A.2 for instance), which is not realistic in practice. Therefore, an interesting perspective to work on is to focus on the even more frequent situation of dose selection in the context of the phase II dose-finding study with a fixed sample size and a balanced design. For this purpose, one could propose a statistical decision framework a little bit simpler than the one mentioned above: utility values would be assigned to the doses themselves, and then indirectly assigned to the decisions at the end of the phase II study: as being equal to the utility value of the selected dose for phase III or a null value if it is decided not to pursue the drug development after phase II. Now the sponsor's problem would be to find the best dose, that is to say, the one having the highest utility. For conducting the analysis and identify the optimal dose, we advocate the use of a Bayesian method, instead of a frequentist maximum likelihood approach: it has the advantage of providing a richer set of dose selection rules and, by definition of the Bayesian approach, allows the sponsor to use external information already available. All these perspectives correspond to ongoing work developed by the authors of this paper.

**Acknowledgement** We would like to thank all the contributors for their helpful comments and suggestions that led to an improved paper.

### Conflict of Interest

*The authors have declared no conflict of interest.*

## Appendix

### A.1. The computation of the Probability of Success

The PoS that we consider for efficacy in our utility functions is defined as follows.

Suppose that  $\bar{\Delta}(d) = \bar{Y}_d - \bar{Y}_0$  is the difference in observed mean effects between dose  $d$  and the placebo in phase III.

A successful phase III trial means that  $\bar{\Delta}(d) \geq z_{1-\alpha} \times \sqrt{2SE^2}$  (assuming without loss of generality that positive values favor the test drug), where  $SE^2 = \sigma^2/(N_3/2)$ , and  $z_{1-\alpha}$  is the  $1 - \alpha$  quantile of the standard Normal distribution.

The expectation of  $\bar{\Delta}(d)$  is equal to  $m(d; \theta) - m(0; \theta)$ ; this difference  $m(d; \theta) - m(0; \theta)$  does not depend

on  $E_0$  parameter.

Our null hypothesis  $H_0$  assumes that  $m(d; \theta) - m(0; \theta) = 0$ . Our statistic of interest is defined as:

$$Z = \frac{\bar{\Delta}(d)}{\sqrt{2SE^2}}$$

Under  $H_0$ ,  $Z$  follows a standard Normal distribution. A unilateral  $\alpha$  level of 0.025 is considered in our calculations: if  $Z > 1.96$ ,  $H_0$  is rejected in favor of  $H_1: m(d; \theta) > m(0; \theta)$ .

Assuming a particular alternative hypothesis  $H_1: m(d; \theta) - m(0; \theta) > 0$ , the true PoS can then be written as:

$$\begin{aligned} PoS(d) &= P_{H_1}(Z \geq 1.96) = P_{H_1}(\bar{\Delta}(d) \geq 1.96 \times \sqrt{2SE^2}) \\ &= \Phi\left(\frac{m(d; \theta) - m(0; \theta) - 1.96 \times \sqrt{2SE^2}}{\sqrt{2SE^2}}\right) \end{aligned}$$

### A.1. Results for U2

In the following results, optimisations of patient allocation to doses and global allocation ratio between phase II and phase III are conducted simultaneously ( $w$  and  $f$  are optimized at the same time).

#### Non optimal

sigmoid	plateau
$w = (0.2, 0.2, 0.2, 0.2, 0.2), f = 0.25$	$w = (0.2, 0.2, 0.2, 0.2, 0.2), f = 0.25$
Go=:88%	Go=:95%
doses= 0.29, 0.68, 0.02, 0.00	doses= 1.00, 0.00, 0.00, 0.00
POS(go)=75%	POS(go)=100%
E(U)= 4370.71	E(U)= 3761.01

#### Optimal

sigmoid	plateau
$w = (0.15, 0.04, 0.30, 0.37, 0.14), f = 0.65$	$w = (0.08, 0.15, 0.33, 0.01, 0.43), f = 0.49$
Go=:97%	Go=:99%
doses= 0.04 0.94 0.02, 0.00	doses=1.00, 0.00, 0.00, 0.00
POS(go)=95%	POS(go)=100%
E(U)= 6502.97	E(U)= 3972.67

Table 5: Optimal versus non-optimal design for  $U2$ , where optimal design consists here in optimizing the patient allocation to doses and the global patient allocation between phase II and phase III simultaneously, Sigmoid and Plateau scenarios

Table 5 is a typical example highlighting the crucial importance of phase II sample size, where the optimal design is allocating more patients in phase II than in phase III, which is not quite realistic in real life.

## A.2. Additional results for U9

Below is the graph of utility expectations (after the sponsor's choice: Go and dose choice) as a function of  $f$ , for the Sigmoid scenario:

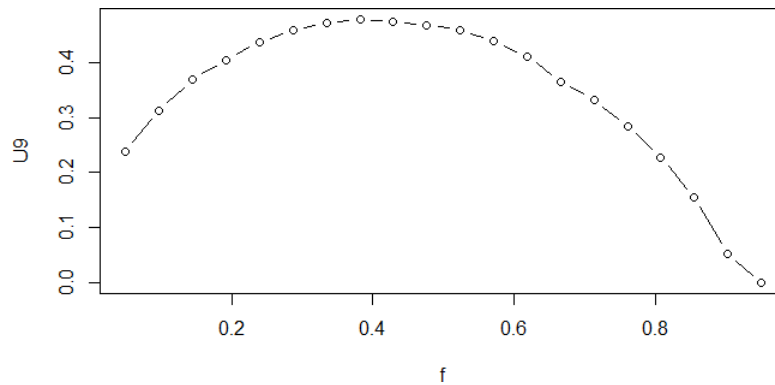


Figure 7: Utility expectations as a function of  $f$ , Sigmoid scenario

Below is the graph of utility expectations (after the sponsor's choice: Go and dose choice) as a function of  $f$ , for the Plateau scenario:

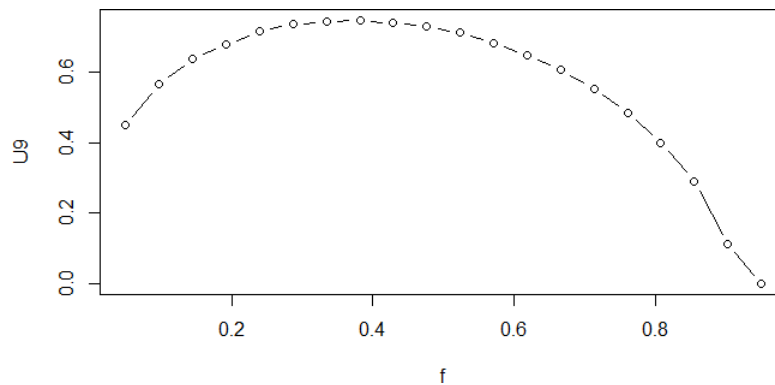


Figure 8: Utility expectations as a function of  $f$ , Plateau scenario

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