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Profit based phase II sample size determination when adaptation by design is adopted

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Background Adaptation by design consists in conservatively estimating the phase III sample size on the basis of phase II data, and can be applied in almost all therapeutic areas; it is based on the assumption that the effect size of the drug is the same in phase II and phase III trials, that is a very common scenario assumed in product development. Adaptation by design reduces the probability on underpowered experiments and can improve the overall success probability of phase II and III trials, but increases phase III sample size enlarging time and cost of drug development, also reducing the potential time on market of the drug under study. In this work, the aim is to build a profit model under the assumption that adaptation by design is applied, in order to compute the dependence of profit from phase II sample size and conservativeness and to appropriately size phase II on the basis of profit behavior.

Methods Recent theoretical results on adaptation by design (viz. conservative sample size estimation) provide the probabilistic distribution of phase III sample size and the probability of launching phase III. The moments of phase III sample size, viewed as a random variable, can be computed, in function of the phase II sample size and of the amount of conservativeness.

Results The modeled revenue depends on: income per patient, annual incidence, time on market, market share, phase III success probability. The modeled cost depends on: fixed cost of the two phases, cost per patient under treatment. Profit is revenue minus cost, and it depends on the random phase III sample size. So profit moments depend on phase II sample size and conservativeness. To consider expected profit and profit volatility is mandatory, in agreement with modern evaluation of

investment performances. The utility, a linear function of profit expectation and volatility, is therefore evaluated. Phase II sample size can be determined on the basis of utility, for example optimizing utility, or achieving a given utility value. An application shows how profit expectation, volatility and utility depend on phase II sample size and conservativeness, and how phase II sample size can be determined.

Conclusion It has been shown how profit and profit utility depend on phase II sample size, amount of conservativeness, launching rule. A suitable setting of these adaptation by design operational parameters can improve profit and increase profit utility. Adaptation by design can be adopted in many different statistical problems. Consequently, the profit evaluations here proposed can be widely applied, together with profit based phase II sample size determination.

Keywords: Adaptation by Design; Conservativeness; Conservative Sample Size Estimation; Phase III Sample Size; Success Probability; Profit; Revenues; Costs; Utility; Phase II Sample Size Determination.

1 Background

Phase III trials are usually planned on the basis of phase II data. The rational modeling of this habit has generated the statistical technique named "Adaptation by Design" (AbD)- this definition comes from Wang et al. [1, 2]. In detail, AbD consists in computing the phase III sample size on the basis of the effect size (ES) estimate obtained from phase II data, where the variability of the latter is accounted for. In agreement with mathematical statistics language, AbD has been called Conservative Sample Size Estimation (CSSE) [3]. In this context, phase II data are not used for phase III confirmatory analysis.

Some Bayesian techniques too, that consider the distribution of the ES posterior to phase II, are applied to estimate phase III sample size, and they fall under CSSE [4]. Although the Bayesian approach can be useful in complex situations (see, for example, [5]), Bayesian sample size estimates often present a very high variability, implying problems in logistics [6]. Then, in this paper, the frequentist approach to CSSE is considered.

CSSE is based on the assumption that the response variable and the ES are the same in phase II and phase III. Apart cancer trials, where endpoints of phase II and phase III are usually different, there are no clinical area restrictions to apply CSSE. Wang et al. [1] argue: "In many cases, we generally explore the appropriate clinical endpoint in the phase II trials". Moreover, Kirby et al. [7] state that in their company (which is one of the world's largest) "the most common scenario assumed in product development is that the treatment effect is the same in both phase II and phase III studies". Then, CSSE can be applied in the context of many clinical trials.

It has been shown [1, 3, 6] that CSSE: on one hand reduces the probability of underpowered phase III and improves the average success probability of phase III; on the other hand it reduces the probability of launching phase III.

Basic settings for CSSE are: the phase II sample size per group (n); the launch threshold of the ES (δ_L); the amount of conservativeness (γ) adopted for estimating the phase III sample size. When these parameters are well set, CSSE can provide a high Overall Success Probability (of phase II *and* III trials) and a suitable precision in planning phase III [1, 3, 6, 7].

In practice, CSSE is a statistical tool to increase the phase III sample size suggested by the ES observed in phase II, and it is based on some probabilistic reasoning (not just on some rules of thumb, such that of discounting the observed ES of, e.g., 90%).

Then, CSSE improves the probability of success of clinical trials (and so the expected revenues) but enlarges times and cost of experimental phases. Therefore, the point is how the balance between higher revenue and larger cost results. In other words, it is of interest how CSSE reflects on profit. Moreover, it is of main interest if a suitable sizing of phase II (i.e. a suitable setting of n) can imply a good phase III planning and a consequent good profit.

Recent simulation based works, considering specific clinical studies, linked sample size estimation to profit [e.g. 8, 9]. Although several aspects of the drug development program were considered, and interesting detailed profit models were adopted, just the expected profit was computed and no concerns to profit variability were provided; moreover, the variability in sample size estimation was not considered, that is, the observed ES was adopted for planning phase III and CSSE was not applied.

The aims of this work are: a) to link CSSE to a profit model, in order to obtain direct calculation of the profit distribution; b) to show how a suitable setting of phase II sample size (n) and conservativeness (γ) can influence and improve profit (i.e. obtaining higher profit expectation and lower volatility) and profit-based utility functions.

2 Materials and Methods

Parallel designs with balanced sampling in both phase II and III trials are considered. CSSE is adopted for sizing phase III on the basis of phase II data, where $h-1$ doses of a certain drug are evaluated, together with a placebo arm. A sample of size n is collected for each arm and D represents the selected dose. The true, and unknown, standardized ES of D is $\delta_t = (\mu_D - \mu_P)/\sigma$ (without loss of generality, σ can be considered equal to 1). $d_n^\bullet$ represents an estimator of δ_t based on phase II data. Being δ_L the threshold of interest for the ES, phase III is launched if $d_n^\bullet > \delta_L$ - this is a simple and general launching rule [1, 3 (Ch.3), 7].

When phase III is launched, two two-arm trials comparing D to placebo are run. It is assumed that phase III ES is still δ_t. The ideal phase III sample size, that depends on the unknown ES, is $M_I = \lfloor 2(z_{1-\alpha} + z_{1-\beta})^2/\delta_t^2 \rfloor + 1$, with standard meaning of α and β, and where z_γ is the γth quantile of a standard normal random variable.

The actual sample size of each phase III group is an estimate of M_I obtained through $d_n^\bullet$, and so based on phase II random samples. To control random variability, a conservative approach is adopted: $d_n^\bullet = d_n - z_\gamma\sqrt{2/n} = d_n^\gamma$ is the lower bound of a one-sided confidence interval for δ_t, with coverage probability γ. Then, phase III (random) sample size is

$$M_n^\gamma = \lfloor 2(z_{1-\alpha} + z_{1-\beta})^2/(d_n^\gamma)^2 \rfloor + 1 \tag{1}$$

Since $P_{\delta_t}(d_n^\gamma \geq \delta_t) = 1-\gamma$, M_n^γ provides underpowered experiments with probability $1-\gamma$. The higher is γ, the higher phase III sample size and the averaged success probability of phase III, provided that phase III is launched. Indeed, at the same time, the higher is γ, the lower the probability to launch phase III (i.e. $P_{\delta_t}(d_n^\gamma > \delta_L)$). In practice, low γs give low success probabilities, and high ones give low launch probabilities. An amount of conservativeness (γ) from 50% to 80% is suggested,

since it often provides the optimal Overall Success Probability, which actually is a concave function of γ [6].

Note that, since phase III is launched only when $d_n^\gamma > \delta_L$, M_n^γ has an upper bound given by $m_{\max} = \lfloor 2(z_{1-\alpha} + z_{1-\beta})^2/\delta_L^2 \rfloor + 1$. Exact formulas for the distribution of M_n^γ are reported in Ch.3 of [3].

3 Results

3.1 Modeling Profit

The profit model is built by referring to [10] and [8]. Basically, profit is the revenue minus the cost.

The revenue depends on: the income realized by treating one patient (i_p), the annual incidence of the illness condition under consideration (ai), the time on market of the drug (t_{mark}), the market share (s), the success probability of phase III (SP_{III}). Since t_{mark} and SP_{III} depend on n and m, the latter denoting the generic sample size of one group in phase III trials, the revenue (r) too is a function of these sample sizes:

$$r(m,n) = \begin{cases} i_p \times ai \times t_{mark}(m,n) \times s \times SP_{III}(m) & \text{if phase III is launched} \\ 0 & \text{otherwise} \end{cases} . \quad (2)$$

In detail, $SP_{III}(m) = \Phi(\delta_t \sqrt{m/2} - z_{1-\alpha})$ (see [3], Ch.1), and the time on market, which depends on: the time horizon of the patent (t_h), the time spent between experimental phases (t_{bp}), the total sample sizes of both phases, the accrual rate (ar), is:

$$t_{mark}(m,n) = \begin{cases} t_h - t_{bp} - (hn + 4m)/ar & \text{if } t_h > t_{bp} + (hn + 4m)/ar \\ 0 & \text{otherwise} \end{cases} . \quad (3)$$

The cost of the whole experiment depends on the fixed cost of the two phases (fc_{II} and fc_{III}) and the cost per patient under treatment (c_p). Being $(h \times n + 2 \times 2 \times m)$ the total sample size, the cost is:

$$c(m,n) = \begin{cases} fc_{II} + 2 \times fc_{III} + c_p \times (h \times n + 2 \times 2 \times m) & \text{if phase III is launched} \\ fc_{II} + c_p \times h \times n & \text{otherwise} \end{cases} . \quad (4)$$

Then, making use of (3) and (2) for the revenue, and of (4) for the cost, the profit is:

$$p(m,n) = r(m,n) - c(m,n) \tag{5}$$

Now, it should be remarked that the actual phase III sample size (M_n^γ) is a random variable, since it is based on phase II samples. Moreover, the behavior of M_n^γ depends on n, on the conservativeness γ, and on its upper bound $m_{\max}$ (which is a function of the launch threshold δ_L). As a consequence, also revenue, cost and profit are random variables whose behavior depend on n, γ and $m_{\max}$. So, the random profit can be denoted by $P_n^\gamma = p(M_n^\gamma, n)$ - for simplicity, the dependence from $m_{\max}$ is not reported.

Hence, thanks to (5) and to the distribution of M_n^γ in (1), the moments of P_n^γ can be computed. The q-th moment is:

$$\mu_q(n,\gamma) = E[(P_n^\gamma)^q] = \sum_{m=2}^{m_{\max}} (p(m,n))^q P_{\delta_t}(M_n^\gamma = m) - (fc_{II} + c_p \times h \times n)^q P_{\delta_t}(d_n^\gamma \leq \delta_L) \tag{6}$$

In particular, the first term in the right-hand side of (6) represents the part of the q-th moment of profit when phase III is launched, where the second term that when phase III is not launched. The first and the second moment of P_n^γ give the mean and the variance of profit.

3.2 Sizing phase II on the basis of profit

Profit is a random variable based on investments, that, in the model here introduced, are represented by cost and time. Then, profit can be viewed as the random performance of an investment. In modern portfolio theory, investment performances are usually evaluated through the classical mean-variance criterion (Markowitz, [11]).

In practice, besides expected profit (μ_1), profit volatility (i.e. the standard deviation $\sigma(P_n^\gamma) = \sqrt{\mu_2(n,\gamma) - \mu_1(n,\gamma)^2} = \sigma_P(n,\gamma)$) should be accounted for. We remark that considering profit volatility goes further [8] and [9].

A suitable investment is characterized by a performance with high expectation and small volatility. Often, the maximum of the former does not match with the minimum of the latter. Then, the utility function (u), which is a linear combination of performance expectation and volatility, is usually adopted to find the subjective best performance. This holds for profit too, so that the utility of profit is adopted

for evaluating profit behavior. Since μ_1 and σ_P depend on phase II sample size n and conservativeness γ, utility turns out to be:

$$u(n,\gamma) = \mu_1(n,\gamma) - \lambda\sigma_P(n,\gamma) \tag{7}$$

The parameter λ represents the subjective aversion to risk: it quantifies how many μ_1 points an investor would pay for one point reduction in σ_P. The higher is λ, the higher the aversion to risk of the investor is. In this framework, investor's role is played by the research sponsor.

Note that when $\lambda = 0$, utility is the expectation of profit. In practice, aversion to risk is important for investors, and this implies $\lambda > 0$. Consequently, σ_P becomes of great interest.

Phase II sample size n can be determined on the basis of utility. At first, note that as n increases, cost increases too, where revenue cannot raise over $i_p \times ai \times t_h \times s$. So, when n tends to infinity, profit decreases and becomes negative. Consequently, it is of interest to find suitable utility solutions for n, where the amount of conservativeness γ can be either given fixed or free of varying.

Then, several criteria can be adopted to determine phase II sample size on the basis of utility. For example, given the risk parameter λ, one can compute the phase II sample size that optimizes utility (viz. n_I). Another possibility consists in computing, given λ and the utility to achieve ($\bar{u}$), the minimum phase II sample size such that $u(n,\gamma)$ overcomes $\bar{u}$ (viz. n_{II}). Both n_I and n_{II} may be computed given γ fixed (e.g. $\gamma = 75\%$).

3.3 Average of cost

Besides profit behavior and phase II sample size determination, the research sponsor may be interested in operational cost c in (4). In practice, the actual cost $c(M_n^\gamma, n) = C_n^\gamma$ is, once again, a random variable. Then, C_n^γ varies from $fc_{II} + c_p \times h \times n$, when phase II only is developed, to $fc_{II} + 2 \times fc_{III} + c_p \times (h \times n + 2 \times 2 \times m_{\max})$, when phase III is launched. On average, the cost is

$$E[C_n^\gamma] = fc_{II} + c_p \times h \times n + 2 \times fc_{III} \times P_{\delta_t}(d_n^\gamma \geq \delta_L) + 4 \times c_p \times E[M_n^\gamma] \tag{8}$$

The range and the mean of C_n^γ might be considered from the sponsor for taking practical decisions that go beyond profit based optimal solutions, some of which has been indicated by n_I and n_{II}.

4 Application

Profit behavior is shown here in a practical context, to remark the dependence of profit from phase II sample size and conservativeness. Then, profit utility is evaluated and phase II sample size is computed following different approaches and under different settings. The amounts of money are reported in thousands dollars.

Assume that $h = 6$ groups are considered in phase II and that the standardized effect size is $\delta_t = 0.5$. In phase III, a power $1-\beta = 90\%$ is desired, with $\alpha = 2.5\%$, giving an ideal sample size $M_I = 85$. The threshold for launching phase III is $\delta_L = 0.205$, giving an upper bound $m_{\max} = 500$ for the phase III sample size estimator M_n^γ. Phase II sample sizes n of 60 and 90 are considered, that, according to [6], are close to the ideal phase III sample size 85.

Now, assume that: the annual incidence of the disease is 50 000, the revenue per patient is \$0.1, the time horizon of the patent is 20 years, the time between phase II and phase III is 6 months, the annual accrual rate is 1200, the market share is 40%, the cost of phase II is \$1 000, that of phase III is \$1 500, and the cost per patient under treatment is \$3.2 (these data are taken from [11]). Then, the mean and the volatility of profit are computed and showed in Figure 1. Of course, a high average of the profit associated to low volatility would be welcome.

As expected, the conservativeness giving best expected profit (μ_1) does not match with that giving lowest volatility (σ_P). Therefore, a uniformly shared optimal solution does not exist: to balance between μ_1 and σ_P, the profit utility should be adopted, that depends on subjective aversion to risk.

Assume that an aversion to risk parameter $\lambda = 0.5$ is chosen, meaning that one would pay 0.5 points of μ_1 for one point reduction in σ_P. The utility functions so obtained are reported in Figure 2.

It can be noted that utility is a concave function of γ. Being γ_{opt} the amount of conservativeness giving maximal utility (i.e. $u(n, \gamma_{opt}) \geq u(n, \gamma)$ for every γ), we have $\gamma_{opt} = 61\%$ and $\gamma_{opt} = 66\%$, with $n = 60, 90$, respectively. Detailed values of utility and profit values are reported in Table 1.

It can also be noted that utility with $n = 90$ is higher than that with $n = 60$: this is not a constant trend, since utility decreases an n tends to infinity; for example, with $n = 1000$ cost is so high that $u(1000, \gamma) < 0$, for every γ.

The determination of the value of n providing the best utility with $\lambda = 0.5$, regardless to γ, gives $n_I = 197$, see Figure 3. Considering that one would adopt the fixed conservativeness $\gamma = 75\%$, the determination of the smallest phase II sample size overcoming the utility threshold $\bar{u} = 18000$, that is, a difference of \$18M between expected profit and half of the volatility is assumed to be of minimal interest, gives $n_{II} = 105$ (Figure 3). The values of $n_\bullet$ with respective utility and profit values are reported in Table 2.

Comparing Tables 1 and 2, remarkable are the small differences between the values of expected profit (i.e. \$22 301, \$23 202) obtained when phase II sample size n_I gives the best utility and those obtained with $n = 90$ (i.e. \$21 827, \$22 938): utility is best with n_I thanks to an approximated 40% reduction in volatility with respect to that with $n = 90$.

Finally, note that with $n = 60, 90$, the maximum of the cost is \$11 552, \$12 128, respectively (see section 3.3). However, since the phase III sample size M_n^γ is often lower than $m_{\max} = 500$, the average of cost (8) is around \$6 300, \$7 100, when $n = 60, 90$, respectively, with small γ-dependent variation.

4.1 Varying aversion to risk, launch threshold, power

To evaluate how results change when the launch threshold δ_L and the aversion to risk parameter λ vary, a second level has been considered for these two settings. The former has been set to $\delta_L = 0.145$ (giving $m_{\max} = 1000$), and latter to $\lambda = 1.5$. Consequently, a total of four different scenarios have been studied.

Table 1 reports utility and profit values with $n = 60, 90$, where Table 2 reports those of the determined sample sizes n_I and n_{II}

In this application, utility and profit measures do not vary a lot when n goes from 60 to 90 and λ changes from 0.5 to 1.5: there are great differences when n is too small with respect to the problem it is apart. For example, when $n = 30$, utility is about 50% of that when $n = 90$.

To improve profit, the power may be set higher, in order to then increase phase III success probability and, so, the revenue. Nevertheless, when $1 - \beta$ is higher, also M_I increases and so does the random phase III sample size M_n^γ, together with the cost. For example, increasing the power to $1 - \beta = 95\%$ (that gives $M_I = 104$), with $m_{\max} = 500$ and $\lambda = 0.5$, the optimal u (i.e. $u(n, \gamma_{opt})$) with respective values of μ_1 and

σ_P, result equal to: \$16 289, \$21 587, \$9 316 with $n = 60$, and to \$19 033, \$22 913, \$7 761, with $n = 90$. Comparing this $u(90, \gamma_{opt}) = 19033$ with that obtained with power equal to 90% (i.e. \$17 557, see Table 1, second line), an increment of 8.4% in profit utility is obtained; the average of cost is around \$7 300, with a increment of 2.8% with respect to \$7 100.

5 Conclusion

In this work, according to the aims claimed in the first section, a model linking Conservative Sample Size Estimation (viz. Adaptation by Design) and profit distribution has been built. The results showed how expectation and volatility of profit and, mainly, profit utility depend on: phase II sample size n, launch threshold δ_L, amount of conservativeness γ. Moreover, a correct adoption of CSSE (i.e. a suitable setting of its operational parameters n, δ_L, and γ), besides increasing the Overall Success Probability [6], can improve profit and increase profit utility - this has been shown through the application in section 4.

Usually, the launch threshold δ_L is defined either by clinical indications, or as a consequence of the maximum sample size imposed to phase III trials. Therefore, profit behavior can be more directly influenced by n and γ. Inverting the latter relationship, phase II sample size n can be determined on the basis of profit, and in particular of profit utility; the conservativeness γ can either remain free of varying, or be given fixed, i.e. by defining in advance which CSSE strategy is to be applied. For example, phase II can be sized in order to optimize profit utility, or to achieve a given level of the latter.

CSSE can be applied in a general parametric framework (including χ^2, t, and F tests) through the estimation of lower bounds of noncentrality parameters (see [3], Ch.5). A general nonparametric technique for CSSE is also available, for k-sample, univariate or multivariate tests (see [6], Ch.9, and [12]). Moreover, CSSE can be applied also when phase II effect size is different from phase III one, by adopting suitable correction strategies [1, 13].

To conclude, CSSE can be adopted in many different clinical contexts (as explained in the first section) and it can be used in many different statistical problems. Then, the profit evaluations here proposed can be widely applied, together

with profit based phase II sample size determination.

The profit model giving (6) can, of course, be improved. For example, safety considerations can be introduced in the analysis of phase II results for the subsequent, eventual, launch of phase III. Also, the market share can be modeled as a function of the results of safety and efficacy observed in phase III. Future works might concern these topics.

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Table 1	Utility and profit values				
settings	n	γ_{opt}	u	μ_1	σ_P
$m_{\max}$ =500	n =60	61%	15362	20401	10078
λ =0.5	n =90	66%	17557	21827	8540
$m_{\max}$ =1000	n =60	66%	17043	21593	9101
λ =0.5	n =90	73%	19026	22938	7465
$m_{\max}$ =500	n =60	55%	5487	20089	9735
λ =1.5	n =90	61%	9168	21557	8259
$m_{\max}$ =1000	n =60	63%	8016	21464	8965
λ =1.5	n =90	70%	11840	22821	7321

Table 1. Utility and profit values in various settings of risk and of upper bound for phase III sample size, with $M_I = 85$ and $n = 60, 90$.

Table 2	Utility and profit values				
settings	n	$\gamma_\bullet$	u	μ_1	σ_P
$m_{\max}$ =500	n_I =197	γ_{opt} =81%	19678	22301	5246
λ =0.5	n_{II} =105	γ =75%	18016	22290	8457
$m_{\max}$ =1000	n_I =178	γ_{opt} =85%	20947	23202	4510
λ =0.5	n_{II} =74	γ =75%	18045	22405	8720

Table 2. Sample sizes determined with two different criteria, together with their respective utility and profit values, for two different upper bounds for phase III sample size, and with $M_I = 85$.

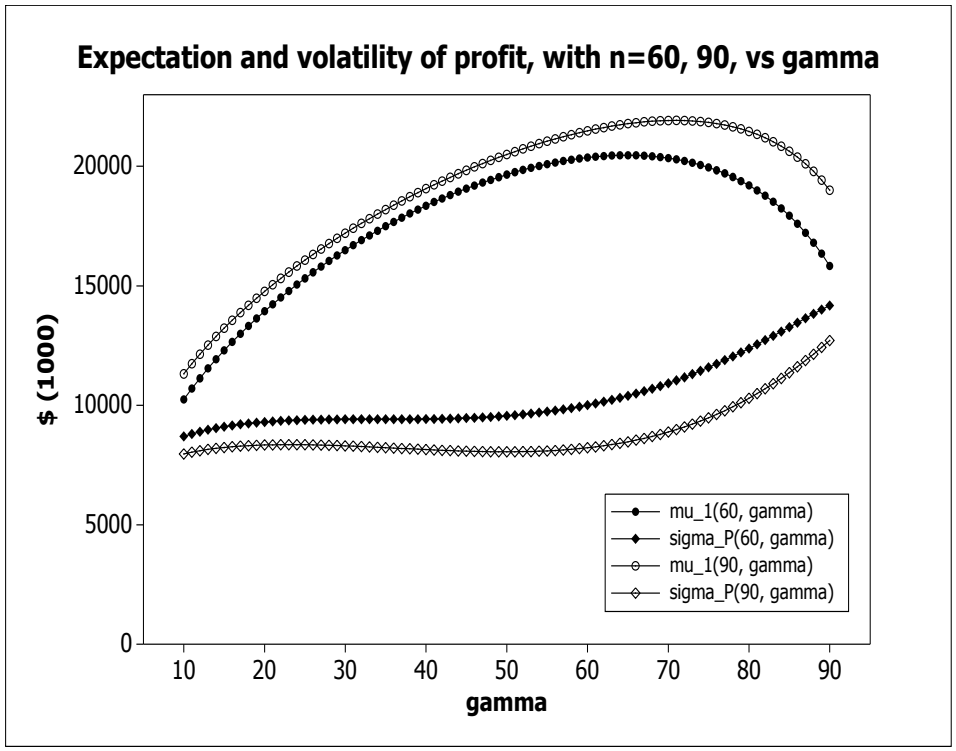

Figure 1: *Expected profit and profit volatility with* $n = 60, 90$, *in function of* γ.

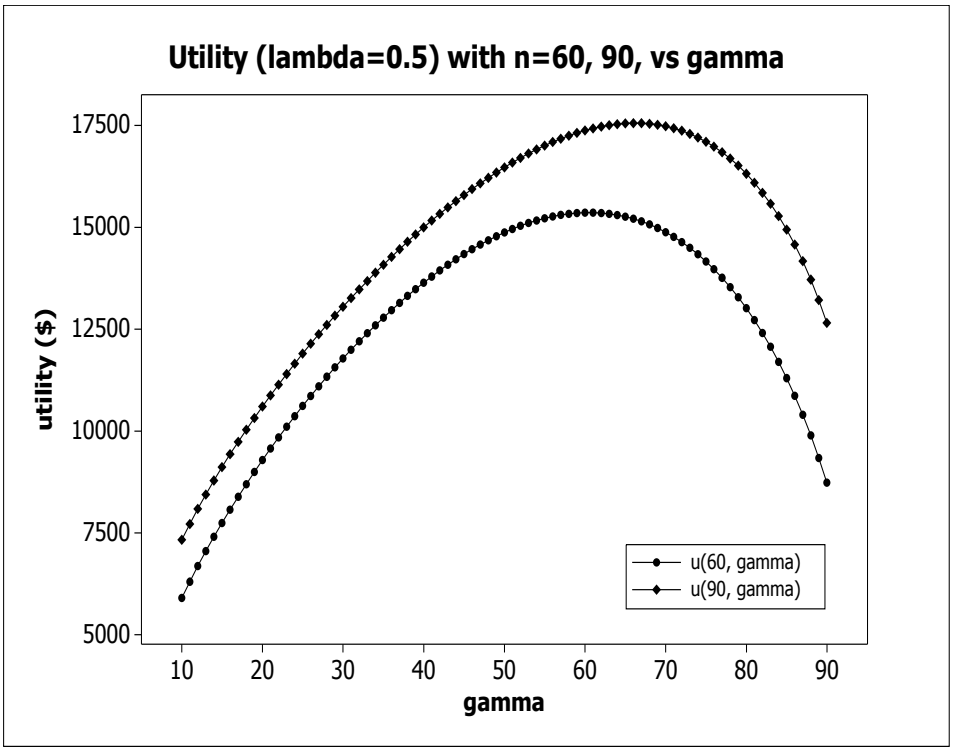

Figure 2: *Utility with* $\lambda = 0.5$*, and with* $n = 60, 90$*, in function of* γ.

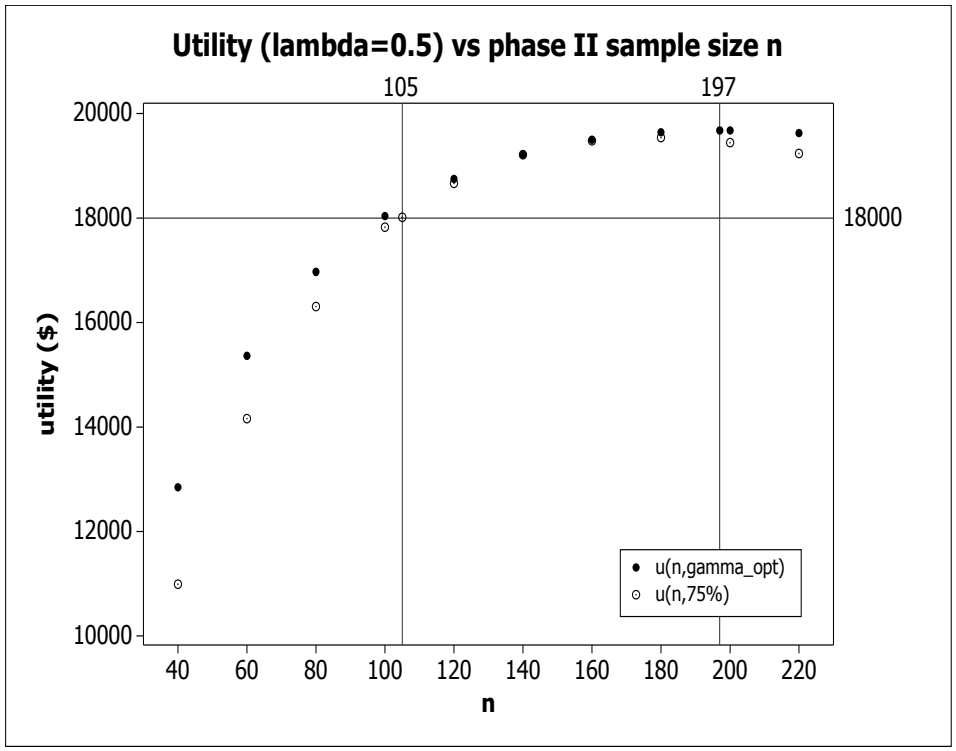

Figure 3: *Utility (maximal and with $\gamma = 75\%$) with $\lambda = 0.5$, as phase II sample size increases.*