A VALUE OF INFORMATION APPROACH TO DRUG DEVELOPMENT DECISIONS

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Abstract

Introduction

The range of healthcare technologies available and the evidence to support their use is generally a result of decisions made by the commercial sector about commissioning clinical trials and other studies, or the termination of development. The appropriate methods to make these decisions are not well described. A real options valuation approach has been suggested. In this paper, we explore the relevance of the real options approach to drug development decisions and investigate its relationship to a value of information approach derived from a Bayesian decision theoretic framework.

Methods

The decision to invest in the collection of information for a drug early in the development process is modelled by simulating Phase III trials from prior information derived from Phase II trials. The model is used to investigate and compare the application of a real options valuation and a value of information approach to this decision problem, and to identify potentially successful or failing development plans. The efficiency of approval regimes, based on frequentist p-values, reimbursement decisions or societal value of information, is explored with reference to the socially optimal quantity of information necessary upon which to base decisions under uncertainty.

Results

This model illustrates that value of information is a generalisation of real options approach and can inform rational decision making in this context. The use of this model to inform commercial development decisions and in the design of efficient regulatory frameworks is illustrated.

Conclusions

A decision theoretic value of information approach has potential value in informing decisions from both a commercial and regulatory perspective.

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1 Introduction

There has been recent interest around newer and more efficient methods to support drugs development.(1) Developing a drug is an expensive endeavour, requiring high investments upfront, with uncertain success. Large financial and commercial losses may occur if a compound fails to be approved for lack of effectiveness. In general, R&D projects in the pharmaceutical industry have low success rates. (2) This ultimately leads to a shortage of socially valuable drugs, since market and commercial strategies may both favour developing drugs with large volume potential markets and little innovative content, or stopping the development of socially important products, yet with potential small markets.

Examples of valuation of investments in specific drug development projects are hard to find. Descriptions of the drugs development process(3) underline the extent to which these decisions are taken based on qualitative information and expert opinion. Although these methods may be of value, a more structured approach based on decision analysis(3) and cost-effectiveness(4) has been advocated.

This paper provides a decision-analytic framework to evaluate stop and go decisions for a new drug in conditions of uncertainty.(5) In Section 1, an example of drug development is introduced. Section 2 presents an option value approach to drug development. By showing its equivalence with Expected Value of Information, this Section provides the economic rationale underpinning the use of decision analysis in drugs development. The latter approach is pursued in Section 3, applying Value of Sample Information, both from a commercial and a societal perspective, to the practical example introduced in Section 1. A framework to compare the efficiency of alternative regulatory regimes is also proposed. Section 4 summarises the merits of the approach and compares our proposed methods to those previously reported in the literature. Section 5 concludes.

2 The drugs development problem

This paper examines the incentives faced by commercial and societal decision-makers (DM) in undertaking stop or go decisions for new pharmaceutical compounds.

A commercial decision-maker faces decisions to commit to developing a new drug (go) or abandon the compound (stop), at a time when the notion of potential revenues for the drug is vague. The DM faces several source of uncertainty, the major of which are the cure rate of the new drug and the likelihood of achieving regulatory approval and profitable market sales. Go decisions involve conducting at least one Phase III clinical trial, which will provide information on clinical effectiveness of the drug. Trials are costly undertakings, with costs disbursed upfront and no salvage value. The DM problem is to raise a business case dependent on whether the new drug will be sufficiently profitable to justify research and development costs, which will be lost or sunk if the drug fails to reach approval. The

problem of valuing information arises then because the agent can actively engage in producing and selecting information, at a cost, rather than waiting for exogenous information to become available.

2.1 An example

To pursue approval, the DM needs then to conduct a Phase III trial to obtain an experimental estimate of the relative risk of certain events with the new drug. Before conducting the trial, the DM holds prior information derived from one Phase II clinical trial with 43 participants in the new drug arm and 40 in the placebo arm. The trial showed a rate of success of 0.51 for the new drug and 0.48 for placebo, a non-statistically significant relative risk of success of 1.08. Based on this information, the DM can characterise the prior distribution for the unknown cure rate θ if a trial with n participants were conducted.

In the relevant constituency, the approval regime is based on a frequentist test of significance. A new drug will be approved if the new drug is more effective than placebo, with statistical significance at a 95% level i.e. a p-value of less than 5%. It is assumed that reaching a significant p-value automatically guarantees approval.

If approved, the new treatment will be used in a population of 30,000 individuals. Although the expected return from the new drug is unknown, the DM believes that the market quota will be directly proportional to the overall cure rate of the drug, i.e. if the cure rate for the drug is 50%, then the market quota for the new drug will be 50% of the eligible population. In this example, we assume sales are only dependent on effectiveness, but independent from the price of the drug, assumed fixed, and from formal reimbursement decisions, for example, by bodies such as the National Institute of Clinical Excellence (NICE) in the UK. Sales are therefore independent from willingness to pay, λ.

The cost of experimenting and producing the new drug is known. Both include a fixed and a variable component.(Table 2-1) Experimentation fix costs include the cost of producing the drug for the trial. The cost of production occurs after the drug is approved.

Quality of life and healthcare costs with and without treatment are also known, both for successful or unsuccessful treatment with either placebo or the new drug. The price of the new drug is £300, whilst the cost of other healthcare use is assumed the same for individuals using the new drug and the placebo, £900.

Finally, social preferences are valued using Net Benefit, based on the costs and effects of the new drug compared to placebo, and a monetary measure for willingness to pay, λ, of £30,000. The data of the drug decision problem are summarised in Table 2-1.

Table 2-1 Summary of data, Drug Development example

	Placebo	New treatment
Effectiveness from phase II trial	19/40	22/21
Relative risk of success	-	RR=1.08, p=0.9094
Prior probability of success	$\theta_{pl} \sim$ Beta (19,21)	$\theta_{tr} \sim$ Beta (22,21)
Cost of drug treatment (price), P_t	-	£300
Other healthcare costs	£900	£900
QALY at baseline	30	30
QALY gain with success	0.4	0.4
Cost of trial C_E	-	Fixed cost: £20,000 Variable cost: £1,500
Cost of production new drug C_P	-	Fixed cost: £100,000 Variable cost: £50
Revenue	-	Proportional to effectiveness, = cure rate of new drug conditional on approval
Population N_{pop}	30,000	
Lambda λ	£30,000	

3 Commercial decision-making and option value

The value of any investment is computed as Net Present Value (NPV) i.e. the discounted future flow of revenues net of costs. Traditionally, NPV is computed assuming pre-set scenarios with fixed future costs and revenues. It has been recognised that these assumptions may poorly account for changing circumstances important when valuing an investment, particularly, the role of risk and uncertainty over future outcomes of an investment. These factors may lead to erroneous investment recommendations.

If traditional methods were used in the drugs development problem, a stop decision would ensue. Given the reported effectiveness of the drug in Phase II, and failing to meet regulatory approval, future revenues would be zero and a stop decision would follow.

The concept of real options(6) was developed from financial options.(7) These are contracts that give the investor the right, but no obligation, to buy a certain stock of shares at predetermined future time, at a set price. Valuing the option to invest is a method to incorporate the value of uncertainty when the DM commits to an irreversible investment. Real options have been applied to various investment problems.(8)

A real option would be valued as follows. An investor is offered a contract to buy a certain stock of shares at a fixed price of K = £200, either now (time 0) or in future (time 1). The cost of buying is thus fixed; however, in reality the value of the stock will change with a certain probability. At time 1, the stock could be worth, for example, £100 or £250, with 0.5 probabilities. For simplicity we assumed no discounting.

The investor aims at finding the optimal strategy to maximise future revenue. Buying today is sub-optimal, since the NPV is negative. The expected flow of future revenue, S = 0.5 *(100+250) = £175 is insufficient to cover the cost of stock, NPV = S – K = -£25. If the investor bought the stock today, he should expect a loss. However, if the investor waited until time 1, he would buy the stock if the price increased to £250. In this case NPV = £25, and investing would be optimal. If the investor could pay up to £25 to buy the right to purchase shares in the future, he would be better off than investing now. This amount is the value of the contract, i.e. the value of the option.

The value of the option is the difference between the NPV of investing today, with uncertain future value of the stock, and the NPV of investing in the future, with perfect information. The economic value of the option derives from the ability of the investor to discriminate between future losses and gains with holding perfect information on the uncertain parameter. By not investing, the investor can set a lower non-negative bound to conditional revenue.

Generalising, given the space of all possible prices Q, a price for a future investment K and a gross revenue S, the value of an option, OV, will be equal to the difference between the expected value of the maximum NPV given the decision to invest at time 1, and the maximum expected NPV given the decision to invest at time 0,

$$OV = E_Q \ [\max (NPV(S, K) , 0)] \ - \max [NPV (E_Q (S-K)) , 0]$$

This formula is equivalent to that of Expected Value of Perfect Information (EVPI). The value of the investment, therefore, is equal to the present value of the potential returns, augmented by the value of future information. This idea underpins the equivalence between the value of real options and EVPI.

This example highlights the nature of the wedge between the 'naïve' NPV and the option value for this problem, i.e. the value of reducing uncertainty in the optimal decision. The value of an investment therefore depends on the value of information. In what follows, option valuation will be applied to the drugs development problem.

3.1 The value of the option to develop a new drug

The value of the option to develop a drug can be obtained from a similar approach. A DM is required to take stop or go decisions for a new drug. With current effectiveness information, the drug would not be approved, with null future stream of revenue; development would be abandoned.

Current information is derived from a single trial; however the probability of success of drug and placebo is a random quantity. Given the known distribution of the cure rate, the DM knows that the drug has a positive probability of being approved and generating a profit. If the DM could sample from the distribution of cure rate for the new drug and placebo, he would obtain information on which samples would lead to approval. The DM does not know which of the samples will occur if he were to conduct a trial in reality, but he can estimate the average probability of approval and the average cure rate for the drug conditional on approval, and then predict the average profitability of the new drug. For example, if the DM could 'sample', he would obtain a probability of approval on average, i.e. 42% of the times, and a relative risk of success given approval, 58%. Average market sales (i.e. individuals) would then be 7,308, and at a price of £300, the expected market value of drug would be £2,192,400.

Table 3-1 Summary of results, option value

Parameter	Probability	Value of the option to invest
Relative risk of drug, given approval	0.58 (a)	
Population	30,000 (b)	
Price P_t	300 (c)	
Probability of approval	0.42 (d)	Total conditional sales TS = (a) * (b) * (d) = 7,308
Total Revenue, given approval		Total conditional revenue TR = (a) * (b) * (c) = £5,220,000
Total expected revenue		Total expected revenue TS * (d) = £2,192,400

In fact, abandoning the drug would be equivalent to forego expected revenue of such amount. If the cost of obtaining more information, i.e. of conducting a trial, were less than this amount, the investor would be equally well, or better off than not conducting the trial. If the investor could calculate the maximum potential revenue of the drug, given perfect knowledge of all the true values of parameters involved in his profit calculation, then the value of the option would be equivalent to the entire sum so calculated. The investor would be equally well off if he could pay up to such amount to pursue approval.

Generalising, the DM holds prior knowledge on the true cure rate of the new drug, the unknown mean parameter θ, and selects the optimal investment t^*_θ to maximise his payoff. With perfect information, the future true probability of success θ would be known with certainty. Since the DM only holds information on the distribution of θ, optimal choices are selected based on the expected value of the option.

A trial of infinite size would attain perfect information. The decision not to experiment is equivalent to foregoing the value of information, the opportunity cost of which increases as information converges towards prior information. The value of the option is then the upper bound to the value of conducting a trial.

In practice, the DM can obtain information on θ by experimentation, seeking a finite quantity of less than perfect information.(9;10) The value of the option to conduct a trial increases with sample size. The value of experimentation is the difference between the opportunity loss from a decision with perfect information and that with imperfect information, i.e. the opportunity loss from choosing the optimal strategy under uncertainty. The optimisation problem for the DM is then to establish which sample size he should pursue to maximise NPV, net of trial costs.

Summarising, the examples above aim to show that decision analysis is a fundamental component of investment valuation under uncertainty. The choice between investing or not, and the timing of investment depends on the status of current information, compared with the ideal scenario where the DM is endowed with perfect information. (9;10)

Option value methods are a special case of more general valuation problems that can be framed as decision analytical problems. This is a structured method to rationally inform choices within mutually exclusive alternatives, given a set of payoffs for each potential course of action, and a choice criterion, selecting the course of action associated with the maximum expected total payoff.(11;12)

We show that, despite decision analysis and option value techniques differ in their assumptions around the origin of information signals, the two methods share the same principles to value the acquisition of information. This is the maximum difference in expected opportunity losses from choosing under perfect or current information.

In the drug development problem, experimentation offers the possibility to compare decisions taken under different information structures than the current in forming a decision, considering all parameters for the decision problem. The following sections will present methods for valuing options to develop a new drug using a decision analytic framework.

4 Decision analytic approaches in commercial and societal decision-making

Decision analysis is underpinned by two broad principles.(11;12) The first, any choice in conditions of uncertainty is associated with measurable opportunity loss from choosing the option that will appear sub-optimal after the decision is carried out. The second, the value of acquiring information is bounded by the maximum opportunity loss from selecting the wrong decision. This is the expected value of perfect information, EVPI.

From a private and a societal perspective alike, a drug development project can be framed as a set of investment/abandonment decisions characterised by several technical, clinical and market

uncertainties, summarised in s set of parameters θ, all of which have an economic (option) value. The case for incorporating clinical uncertainty in such valuation is clear. For example, uncertainty may exist around optimal dosage, treatment protocols, treatment effectiveness, etc. The probability of approval is compound-specific and depends on the characterisation of any of these uncertain parameters.

The characterisation of the behaviour of decision-makers and regulatory constraints is also essential. The success of a trial can be assessed using frequentist rules; however, approval only acts as a constraint on the volume of sales. In practice, diffusion of drugs is mediated by decisions of doctors and policy makers, in general based on practice guidelines that make use of cumulative evidence of effectiveness. Such process can be incorporated using the overall, or posterior, estimate of the overall cure rate of the drug.

The value of a new drug to developers and society can then be estimated using specific payoffs, NPV for a commercial DM and net benefit (NB) for a societal DM.

Within this framework, the valuation of an investment requires methods capable of incorporating incremental information accumulating through trial phases, and to provide a measure of the value of information at the start and at the end of each phase.
Bayesian decision analysis approaches are required since the current scientific paradigm based on the frequentist p-value does not allow updating information in decision-making.(13)

Using decision analytical techniques, option value approaches can be extended to incorporate a complete characterisation of uncertainty. Bayesian approaches offer the flexibility to incorporate information around such uncertainties, both as prior information and as updated information used by various decision makers to take decisions, as experimentation or other research is carried out on any or all of these parameters. Further sources of uncertainty may arise, such as market quotas, drug price, quality of life, cost of care, etc, all of which can be incorporated in the drugs development problem in a similar way.

An important aim of such model would be to provide indications around the optimal quantity of information that the investor needs to acquire. Taking continuation or halting decisions when the value of information falls below a certain threshold, the private decision maker can choose between investing in the new drug, collecting more information before undertaking investments in experimentation, or abandoning the development of the drug altogether.

We assume a drug development decision problem modelled as a comparison of the value of a new drug and one pre-existing treatment, or placebo.
Given a prior probability of success for treatment, θ_{tr} and placebo, θ_{pl}, distributed as a beta distribution function with parameters a=r, b=n-r, the probability of success for treatment and placebo can be predicted from the conjugate binomial distribution,

$$\tilde{s}_{pl} = \tilde{r}_{pl} / n_{pl} \quad \text{and} \quad \tilde{s}_{tr} = \tilde{r}_{tr} / n_{tr}$$

where $\tilde{r}_{tr} = \text{bin}(n, \theta_{tr})$, $\tilde{r}_{pl} = \text{bin}(n, \theta_{pl})$ and $n = n_{tr} + n_{pl}$ are the cure rates for treatment and placebo in a trial with n sample size.

The drug will be approved if for each realisation of the potential trial results, the frequentist approval rule is satisfied,

$$H_0 : \theta_{tr} = \theta_{pl}$$

$$\varphi_\theta = f(\theta_{tr}, \theta_{pl}) \sim X_1$$

$$\Phi_\theta = p(-\Phi_\theta < \varphi_\theta < \Phi_\theta) <= \alpha, \ \alpha = 95\%$$

Therefore the probability of approval will be equal to $p_a = p_a(\Phi_\theta, \theta)$.

The problem of the investor is then to establish whether the value of proceeding to develop the new drug conducting a trial justifies the investment. As in option value, the acquisition of additional information aims to reduce technical uncertainty in relation to sunk costs,(10) given a set of prices for the drug.

From the commercial perspective, the NPV from the investment conditional on approval is

$$V(t_{com}, P_t, \theta) = \theta_{tr} N_{pop} * p_a(\theta) * P_t - C_P$$

assuming no discounting.

The optimal investment decision t* maximises expected present value of the stream of future net revenues,

$$V(t^*_{com}, P_t, \theta) = \text{Max}_t \ E_{,\theta,P_t} [V(t, P_t, \theta)]$$

However if the DM had perfect information, he would choose the optimal decision $\tilde{t}$ to maximise the expectation of the maximum NPV, when θ is observed perfectly,

$$V(\tilde{t}_{com}, P_t, \theta) = E_{\theta,P_t,} \max_t [V(t, P_t, \theta), 0]$$

The EVPI or the value of the option from a commercial perspective would be equal to

$$EVPI_{com} = E_{\theta,P_t,} \max_t [V(t_{com}, P_t, \theta), 0] - \max_t E_{\theta,P_t,} [V(t_{com}, P_t, \theta), 0]$$

From the social DM perspective, the optimal decision t* will maximise the expected net benefit considered at a particular value of lambda,

$$E_\theta NB(t^*_{soc}, \theta) = \max_t E_\theta NB(t, \theta)$$

assuming that the decision is carried out under the prior distribution of θ.

If the DM had perfect information, he would choose the optimal decision $\tilde{t}$ after having observed the true values for the parameter θ, under the predicted posterior distribution. The expected payoff for the decision would be the expectation of the maximum payoff over the joint distribution of θ,

$$E_\theta NB(\tilde{t}_{soc}, \theta) = E_\theta \max_t NB(t,\theta)$$

EVPI would be equal to the difference of these two quantities,

$$EVPI_{soc} = E_\theta \max_t NB(t,\theta) - \max_t E_\theta NB(t,\theta)$$

The value of a trial lies in the reduction in uncertainty in predicted sales, form a commercial perspective, or net benefit from a societal perspective, via providing more information on a particular parameter. The value of reducing uncertainty should be sufficiently large to compensate for the cost of a trial.(9;10;14)

Given the optimal decision under the prior distribution of θ, t*, and the optimal decision under the posterior distribution, $\tilde{t}$, the value of information obtained from a study D with sample size n, incorporating information around the parameter θ is equal to(15)

$$EVSI_{com} = E_D \max_t E_{\theta/D,\, P_t} [\, V(t, P_t, \theta) - C_P), 0\,] - \max_t E_{\theta/D,\, P_t} [\, V(t, P_t, \theta) - C_P\,]$$

for a commercial decision maker and

$$EVSI_{soc} = E_D \max_t E_{\theta/D} B(t,\theta) - \max_t E_{\theta/D} B(t,\theta)$$

for a societal decision-maker.

The expected cost of performing an experiment of size n, $C_E = C_E(n)$ is usually fairly easy to compute. In general this will be composed by a fixed component and a variable component for each participant into a trial, and can be extended to include opportunity costs of further experimentation.

The net benefit of sampling will be equal to the value of sample information net of the cost of experimentation,

$$ENBS_{com}(n) = EVSI_{com} - C_E(n)$$
$$ENBS_{soc}(n) = EVSI_{soc} - C_E(n)$$

The optimal sample size will then be equal to

$$n^*_{com} = \max_n [\, ENBS_{com}(n)\,]$$
$$n^*_{soc} = \max_n [\, ENBS_{soc}(n)\,]$$

Therefore, the DM should proceed take a go decision if $n^* > 0$.

4.1 Characterising the drug development decision

In this paragraph, this method is applied to the drug development example (2.1). A simulation of 10,000 trials was run using R, to assess the probability of approval and the optimal sample size for continuation from both the commercial and societal DM.

4.2 Commercial decision-making

We calculated the probability of approval for a trial sample sizes between 10 and 1,000. Given a frequentist approval rule, the new drug would be approved on average between 4.6% (trial size=10) to 48.3% of the times (trial size = 1,000) (Figure 4-1).

For a commercial DM, given a drug price of £300, the investment would then be associated to positive average net revenue of £2,002,779. In this example, this is also equal to the value of perfect information. (Figure 3-2) Given the cost of conducting a trial, the commercial DM would then compute the expected net benefit of sampling for each sample size and then select the optimal sample size n^*_{com} = 300, corresponding to a maximum ENBS of £1,073,985 and a trial cost of £470,000 (Figure 3-2).

4.3 Societal decision-making

For a societal DM, given a price of the drug of £300 and a lambda of £30,000, the total EVPI for the drug development problem £13,500,690. The new drug would be socially undesirable for lambda below £2,000, where the EVPI would be very close or equal to 0. For a value of lambda=£30,000, the optimal sample size n^*_{soc} would be 450 with $ENBS_{soc}$ (n^*_{soc}) = £12,239,779 (Figure 4-4).

4.4 Comparing commercial and societal decision-making

As lambda increases, the societal net benefit of sampling increases, but remains constant for the commercial DM. This is the result of the maximisation problem for the commercial decision-maker being independent from willingness to pay.

For some low values of willingness to pay of the societal DM, the commercial DM may pursue drugs development decisions that are not socially desirable. Over these ranges of lambda, the commercial DM will maximise his payoff by conducting research whilst society would be better off if the drug would not become available. This is illustrated in Figure 4-5 for lambda less than £2,000, where societal, but not commercial, EVPI and ENBS are null. The reverse is likely to happen for high WTP of the societal DM, where society would value information around a compound whilst commercial DM would have an incentive not to produce information to a socially desirable level since commercial ENBS would be low compared to the optimal societal sample size, for example for lambda=£20,000 (Figure 4-5 and Figure 4-6).

Figure 4-1 Probability of approval, by sample size

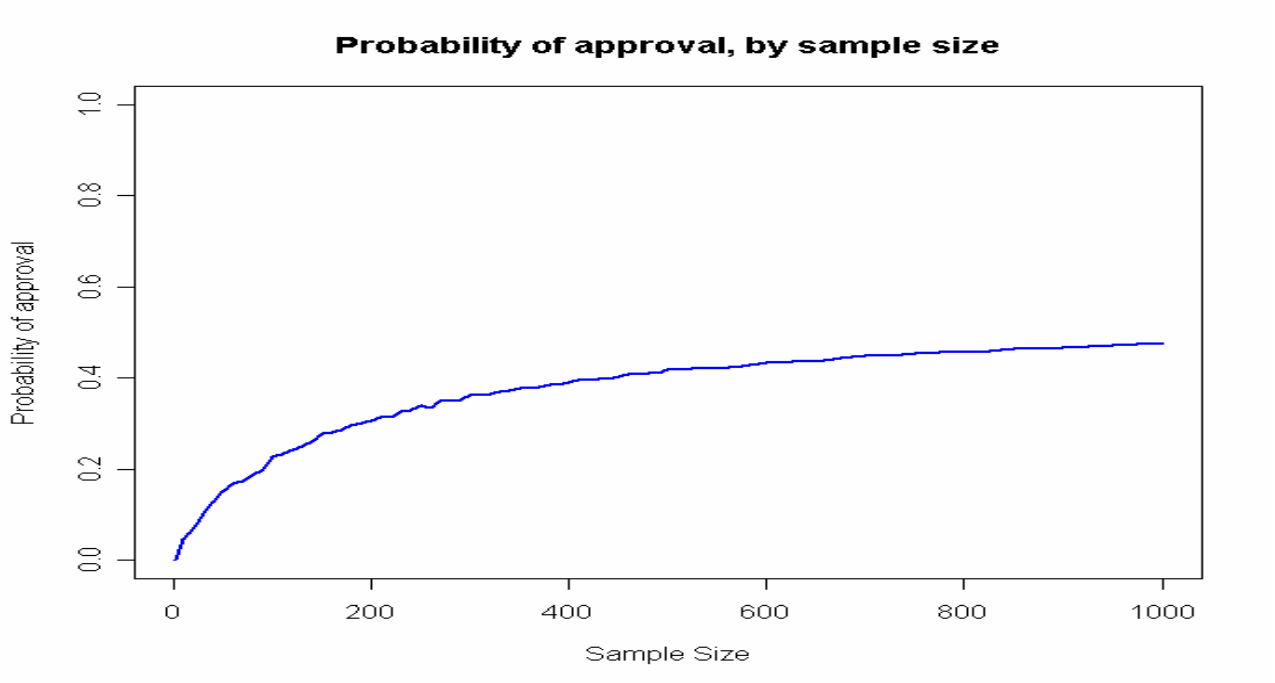


*Figure 4-2 Commercial EVSI (red line), Cost of sampling (black dotted line) , ENBS (blue line), by sample size, at price=£300. Vertical dotted line = n**

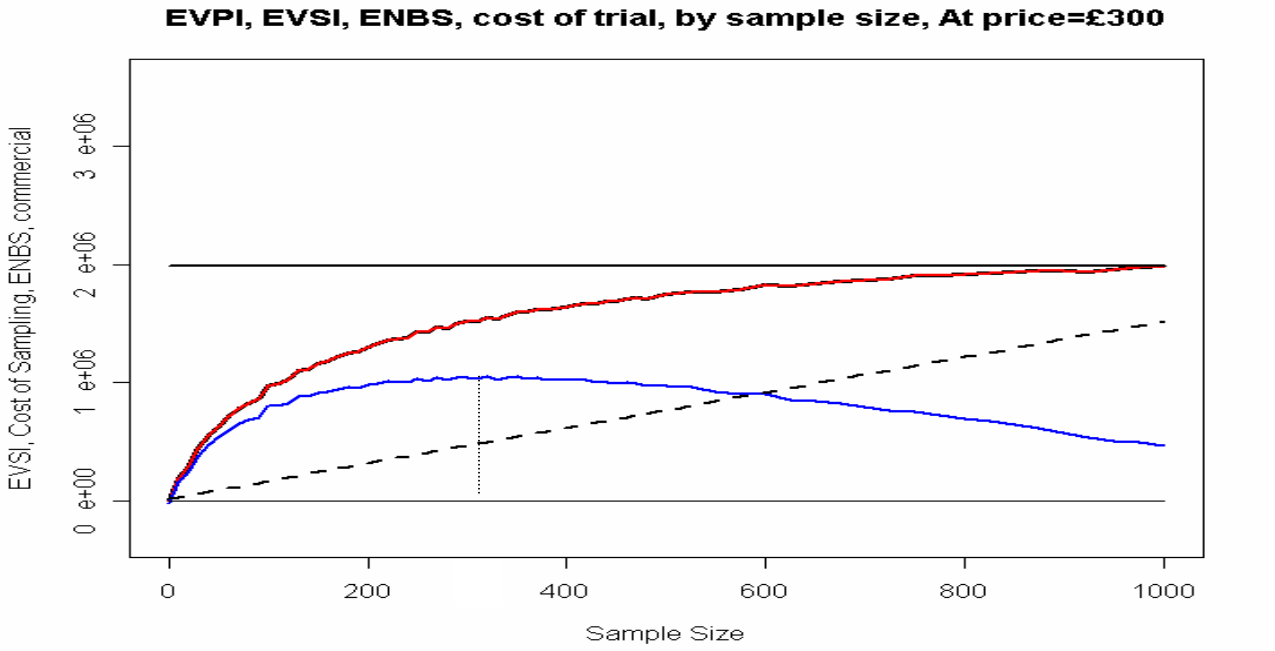


Figure 4-3 Societal EVPI, by willingness to pay (lambda)

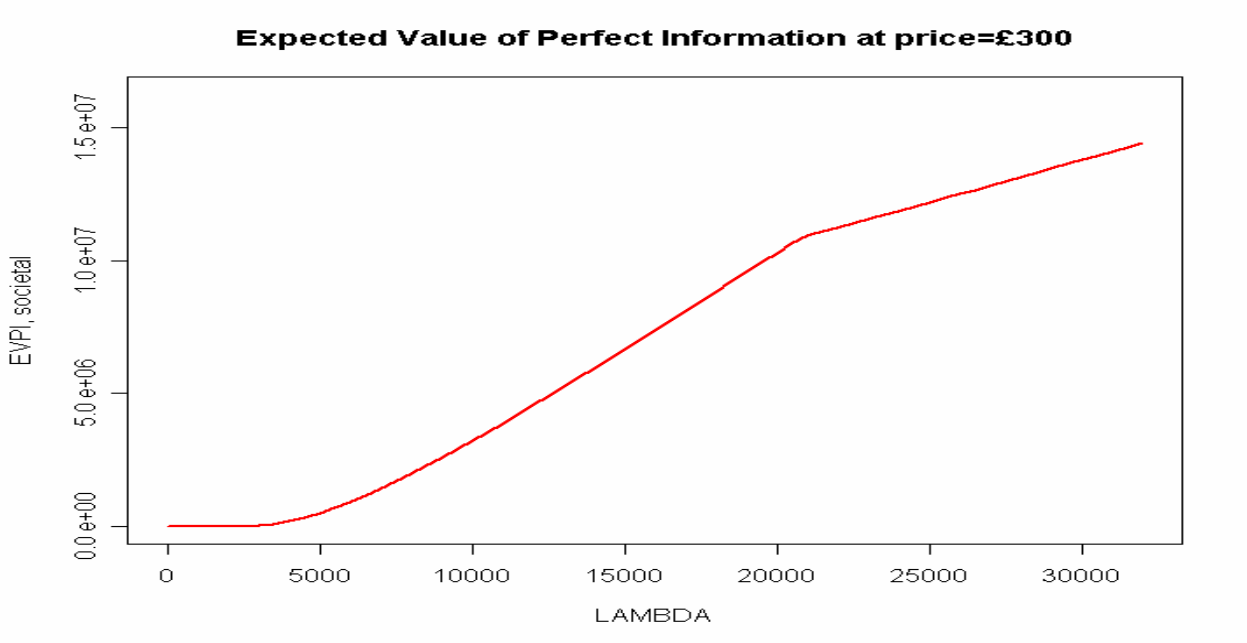
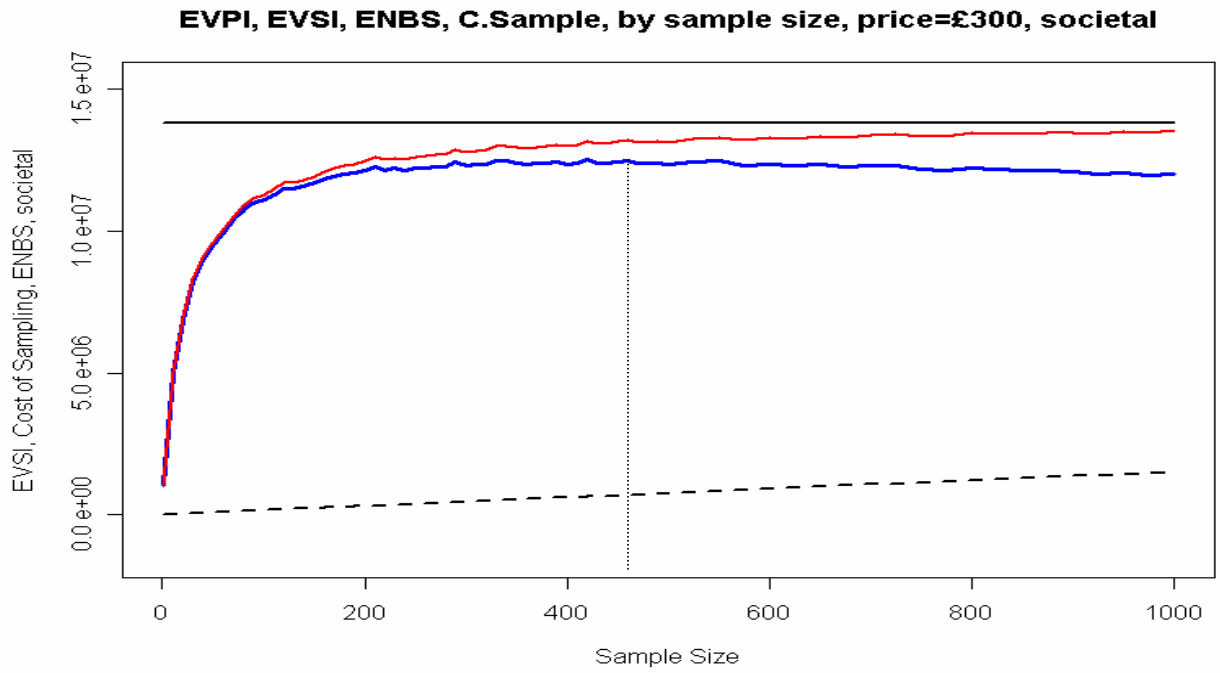


*Figure 4-4 Societal EVSI (red line), CS (black dotted line), ENBS (blue line), by sample size, at price=£300. Vertical dotted line = n**



Despite optimal societal and commercial sample size can be equal (the intersection point in Figure 3-6), in general they differ, since no implicit condition exists that would equalise the incentives of the two DMs.

For any sample size of a potential trial, it is then possible to compare the residual opportunity loss for one decision maker, i.e. societal, by calculating the opportunity loss associated with the availability of a quantity of information set by the other decision maker, i.e. commercial, based on the quantity

$$\pi(\theta) = ENBS_{soc}(n_{soc}) - ENBS_{soc}(n_{com})$$

At the optimal sample size of both,

$$\pi(\theta) = ENBS_{soc}(n_{soc}^*) - ENBS_{soc}(n_{com}^*)$$

In this example, $\pi(\theta) = £255{,}616$. This quantity can be interpreted as the deadweight social loss associated to the particular regulatory regime considered here, i.e. frequentist approval and no assumption or restriction on reimbursement.

In this framework, the function $\pi(\theta)$ could be used to evaluate the performance of regulatory regimes. In particular, given the objective of the social DM of maximising health outcomes, the socially optimal regulatory regime will be such that

$$\pi^*(\theta) = \min_{\theta}(\pi(n_{soc}^*, n_{com}^*, \theta)) \geq 0$$

Figure 4-5 EVPI (red line) , societal ENBS at optimal sample size (blue line) commercial ENBS at optimal sample size (black dotted line) , by willingness to pay (lambda)

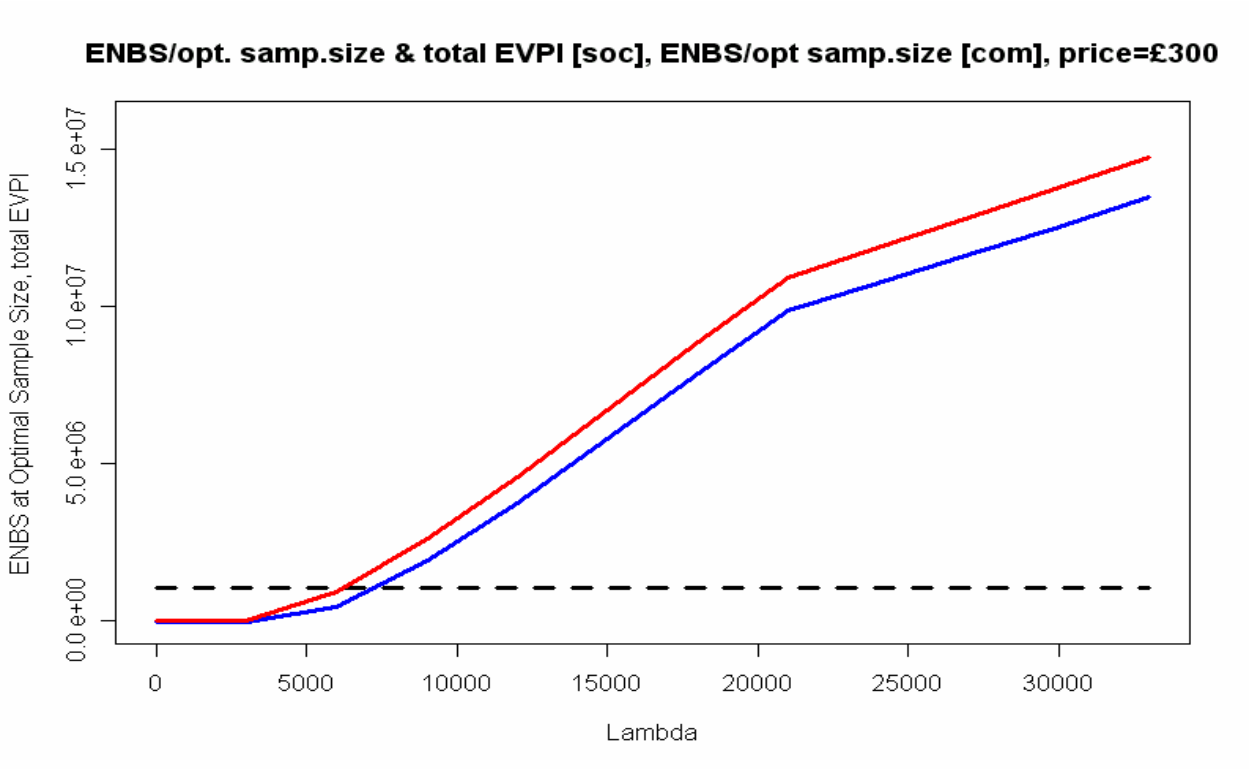
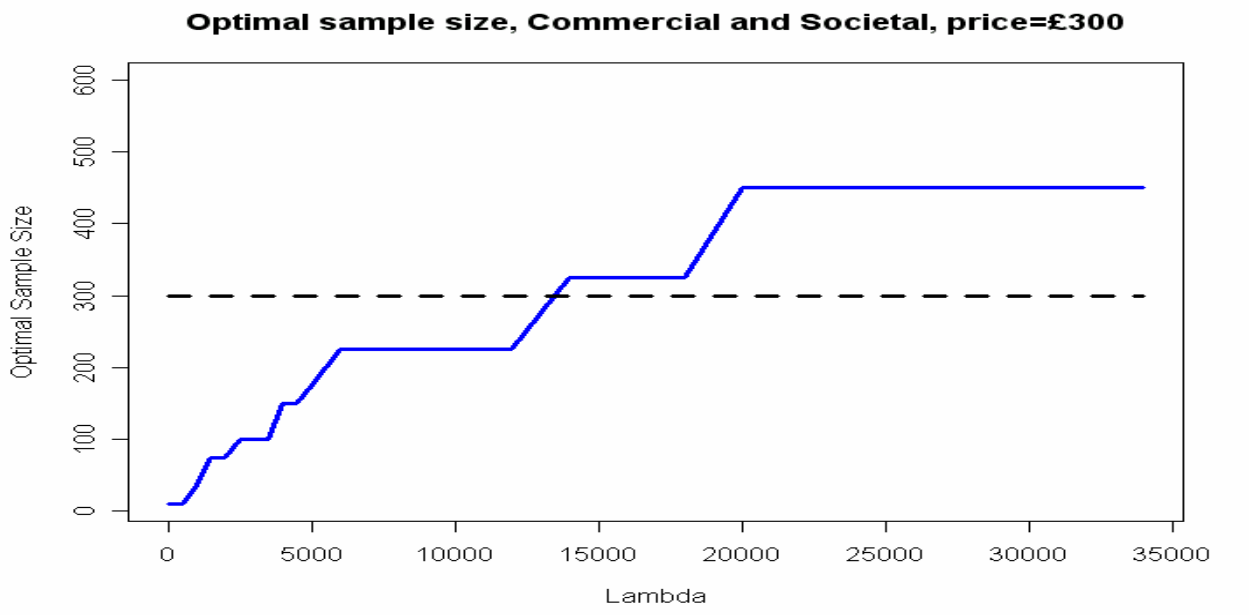


Figure 4-6 Optimal sample size commercial (black dashed line) and societal (blue line), by willingness to pay (lambda)



5 Discussion

This paper is about the valuation of a drug development project using value of information.

Starting from a very simple stylised real options example, we showed that methods to valuate investments based on options and on expected value of information are equivalent. The two methods use the same monetary valuation of the value of pursuing the optimal quantity of information under uncertainty, and equally conclude that the optimal amount of information is equal to the difference between expected and current value of information. This equivalence provides the economic foundation for using Bayesian Value of Information to evaluate the social and commercial value of investing in new pharmaceutical compounds.

Attempts to model Research & Development decisions in the pharmaceutical sector are available from the literature.(16-20) For example Ding et al(17), Blau et al(18), and Rogers et al(21) modelled the drugs development pipeline. These studies were conducted both from the perspective of internal development divisions and to establish whether a pharmaceutical company should buy licensing options from a drug developer. In both cases, the studies aimed to establish optimal conditions for disbursing funds to conduct or subcontract development research at the start of Phase I, II or III trials, and decisions around withdrawing funding at the end of each development Phase, should the profitability conditions of the project change.

These examples are generally formulated as a resource allocation independent from experimentation, given a certain portfolio of compounds and a final market payoff, and use real option value to incorporate the joint effect of uncertainty(21) and decision flexibility.

Drugs development is modelled as a sequence of investment/abandonment decisions dependent on technical and market uncertainty, characterised as stochastic volatility. The development problem is framed as a decision tree with a compound moving across Phase I, II or III trials of fixed duration. Constant probability of achieving technical success and risk neutrality across projects is also assumed.

At the beginning of each experimentation Phase, the investor is faced with a decision to continue experimentation or to abandon the compound, given the value of the project accrued in previous phases. Given the prior present marketing value of drug, the optimal decision is selected maximising the (posterior) present value of the payoff, assuming that uncertainty in market volatility resolves over time. The resolution of uncertainty is assumed exogenous, so can only be accrued by 'waiting'.

These models are innovative in the valuation of investment projects, moving away from a view of profitability as net present value of cash flow, including the opportunity costs of information in development decisions. However, they can only inform cash-flow decisions around timing of disbursement from a single payer perspective, rather than allocation problems for research resources, since they do not consider the role of regulatory arrangements and of clinical uncertainty.

An explicit assumption of these models is that the valuation ratio is constant across projects, with constant optimal licensing time. They also implicitly assume spread of investment risk, assuming an average probability to achieve licensing. In practice these assumption are violated. For this reason, these models are unlikely to inform private allocation decisions, or public allocation and regulatory functions. Ultimately, private decisions should only be informed by models that incorporate current approval arrangements, whilst model failing to do so can hardly be of value in selecting compounds for experimentation.

These models do not consider the endogenous relationship between disbursements and the accumulation of experimental results. Rather, they assume abandonment or continuation decisions dependent on random variations of context factors, such as market profitability. Variations in market conditions reflect stochastic variability rather than uncertainty around parameters of the decision problem, whilst a correct characterisation of the decision problem requires the introduction of a loss function, commercial or societal, and updating of uncertain parameters as knowledge accumulates.

Summarising, despite the intuition that the value of drug development projects requires framing the value of uncertainty in the decision, the various assumptions underpinning these models make it difficult to support their use for project selection purposes.

We believe Bayesian decision analytic approaches offer a more thorough method to assess the value of drug development. Using a stylised example and Value of Information, we proposed a framework to identify optimal conditions under which a new drug should be developed, with reference to research and development decisions from a commercial and a societal perspective. We compared the incentives of commercial and societal decision makers in producing socially optimal quantity of research, based on Expected Value of Sampling information. We then proposed an initial framework to evaluate regulatory approval and reimbursement arrangements, comparing opportunity gains and losses associated with the production of information in support of decision making given particular regulatory rules.

The proposed framework is rather approximate. In particular, we relied on several simplifying assumptions.

We considered a regulatory regime limited to approval, and based on a frequentist test of hypothesis. We also considered one single trial to be fed in the regulatory process, and we assumed that research would be limited to one particular parameter, one treatment, and did not consider either the role of other possible regulatory arrangements.

Clearly, a more realistic model would consider more articulated requirements from regulators, i.e. more than one trial, compared to more than one other drug or treatment, with more than one endpoint included in clinical studies.

Reimbursement regimes are another substantial omission from this example. In particular, we have limited the use of Net Benefit to the valuation of societal benefits from the new drug. More realistic descriptions of the approval and reimbursement process are certainly required to apply this framework to real case studies, and this extension will be pursued in the near future.

We have also considered a rudimentary description of commercial payoffs. In particular, we have considered market sales as a function of effectiveness of the drug. As for any other good, the volumes of sales for a drug are in practice dependent on its price. Realistic models aiming to inform commercial R&D need to incorporate a demand function for the drug. More importantly, the price of the drug is likely to be a parameter for the decision-maker, more than a constant in the decision problem, since the pursuit of the optimum commercial decision is likely to be highly dependent on price-setting arrangements. Therefore, we believe that pricing, optimal sample size n* and stop and go decisions are interdependent decisions and as such should be modelled.

This extension will also be pursued in the near future.

However we believe the most important characteristic of our approach is in its potential to be used to evaluate regimes not currently implemented. A more substantial extension of the model would be required to include additional regulatory requirements, such as joint approval-reimbursement regimes, approval based on optimal sample size, approval based on reimbursement and perhaps, the use of Bayesian adaptive trials in the regulatory process. The inclusion of reimbursement decisions would introduce a relationship between commercial payoffs, cost-effectiveness and willingness to pay of the societal DM. Pricing and sample size decisions from a commercial perspective, on one hand, and willingness to pay and social optima on the other hand would then be strictly interrelated.

6 Conclusion

The framework developed here is simple, but suitably expanded, can provide flexibility to evaluate a range of regulatory regimes, both currently in place and for potential development in the future, and a range of reimbursement regimes.

The social welfare associated with alternative approval and reimbursement arrangements has not been considered before. The assumption that each regulatory decision can be taken within the framework of objectives proper to the specific regulator, and can then be recomposed into a more general pursuit of the optimal decision within the larger societal perspective, has implicitly underpinned various types of rules in use.

The use of decision analysis allows extending the regulatory framework to consider the optimality of regulation under two aspects, the choice of the quantity of experimentation and the use of social costs and benefit of experimentation to achieve socially desirable research allocation, in the context of drug development and approval.

In a budget-constrained world, the DM would aim to minimise financial and social loss ensuing from his decisions. The number of individuals, and hence the cost, of a trial should be conditional on the quantity and value of information in reducing uncertainty in the decision at the socially optimal level. This is achieved with the extension of (any) regulatory process to include a decision function based on the value of the information.

As decision making and funding of research becomes the jurisdiction of several bodies, the framework provided here allows to set research priorities and allocations in an integrated fashion. The potential of this approach is in avoiding socially wasteful duplication of compounds, and under-funding of socially relevant research and production of new pharmacological compounds.

If research and development were to be under the jurisdiction of a unified body, then our approach would provide a unified framework for setting research priorities coherent with social and commercial preferences.

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