HEALTH ECONOMICS
Health Econ. **8**: 269–274 (1999)

HEALTH ECONOMICS LETTER

BAYESIAN APPROACHES TO THE VALUE OF INFORMATION: IMPLICATIONS FOR THE REGULATION OF NEW PHARMACEUTICALS

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SUMMARY

The current regulation of new pharmaceuticals is inefficient because it demands arbitrary amounts of information, the type of information demanded is not relevant to decision-makers and the same standards of evidence are applied across different technologies. Bayesian decision theory and an analysis of the value of both perfect and sample information is used to consider the efficient regulation of new pharmaceuticals. This type of analysis can be used to decide whether the evidence in an economic study provides 'sufficient substantiation' for an economic claim, and assesses whether evidence can be regarded as 'competent and reliable'. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS — Bayesian decision theory; the value of information; statistical methods

INTRODUCTION

The regulation of new health care technologies is founded on a classical or frequentist view of probability where efficacy and safety must be demonstrated in one or more clinical trials at a level of significance and power established by precedent. Until recently it appeared that the United States Food and Drug Administration (FDA) would apply a similar standard to all comparative health economic claims, requiring 'substantial evidence' typically demonstrated 'by two adequate and well controlled clinical trials' [1,2]. However the FDA Modernization Act [3] amends the standard for health economic claims to 'competent and reliable scientific evidence'. What constitutes competent and reliable evidence is not yet clear, but Bayesian decision theory and an analysis of the value of information can be used to decide whether the evidence in an economic study is 'sufficient' substantiation. Indeed it can be used to establish an efficient regulatory framework, based on an assessment of the value of additional information.

ARBITRARY REGULATION

Current regulatory regimes can be described as arbitrary for three reasons. First, the standard of demonstrating efficacy or cost-effectiveness at arbitrarily selected levels of significance (α) and power ($1-\beta$) relies on a power calculation where the optimal sample size is determined by α, β and the difference in outcome that is deemed to be worth detecting (δ_r) [4,5]. If δ_r is not well-defined

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Contract/grant sponsor: Harkness Fellowships of the Commonwealth Fund of New York
Contract/grant sponsor: Harvard Center for Risk Analysis

CCC 1057–9230/99/030269–06$17.50

Received 17 August 1998
Accepted 7 December 1998

or chosen in an arbitrary way then sample size will also be arbitrary. Unfortunately there is little guidance for selecting δ_r and any improvement in either effectiveness or efficiency will be worth detecting when the marginal cost of detecting such a difference is excluded for the analysis.

The traditional power calculation does exclude the marginal cost of sampling and implicitly places an infinite value on the benefits of sample information. This leads to either unbounded or arbitrary sample sizes; consequently regulation based on this calculation demands either infinite or arbitrary amounts of information. In practice the power calculation can be 'reversed' by selecting a sample size that is acceptable to the analyst or sponsor and then solving for δ_r that provides the specified α and β.

Second, the type of information demanded by regulatory regimens is not directly relevant to the decisions of 'a formulary committee or similar entity . . . [or in] the section of drugs for managed care or other similar organisation' [3]. Useful information for decision-making should take the form p[hypothesis|data] but the information provided by a traditional clinical trial takes the form p[data|hypothesis] which by itself provides little useful information to decision-makers. The issue is analogous to measures of diagnostic accuracy such as sensitivity and specificity which are only useful when revising a prior probability of disease to establish predictive values [6]. Almost all users of the results of clinical research and many analysts wrongly interpret the p-value from a clinical trial as p[hypotheis|data] rather then p[data|hypothesis] [7]. This reflects the difficult interpretation and questionable utility of the frequentist approach [8]. Indeed it is only by taking a Bayesian view that useful probability statements such as 'there is a probability of 0.8 that the net benefit of intervention A is greater than the net benefit of intervention B' can be made.

It is not surprising that most users and analysts take an implicitly Bayesian view of probability and interpret p[data|hypothesis] as p[hypothesis|data]. However, this interpretation requires an uninformative (and often improper) prior which is no less subjective than one that contains information. For example, when considering the approval of a new pharmaceutical within an existing therapeutic class or the off-label use of an approved drug for other indications or patient groups, the notion that we have no prior information about efficacy, safety and efficiency is simply not credible. In these circumstances the implicit assumption of an information-less prior is not only profligate and inefficient; it clearly has tangible costs in terms of lives and life years forgone as approval decisions are delayed.

Finally, any regulatory regimen that demands the same standards of evidence in all circumstances and across all technologies irrespective of any evidence already available, the size of the patient population that could benefit from the new technology, and the costs of gathering more information simply cannot be efficient. These issues seem to be recognized in the more recent FDA legislation including a 'fast track' approval in some circumstances [9], and a definition of competent and reliable evidence which references the Federal Trade Commission's standards:

> '. . . a reasonable basis [for a claim] depends . . . on a number of factors relevant to the benefits and costs of substantiating a particular claim. These factors include: the type of product, the consequences of a false claim, the benefits of a truthful claim, the costs of developing substantiation for the claim . . . ' [10].

This standard of evidence requires explicit consideration of the marginal benefits and costs of acquiring additional information but no method for estimating these costs and benefits has been suggested. A Bayesian approach to the value of information does provide such a method and a framework which defines a claim as substantiated when it is not efficient to gather any more information.

EFFICIENT REGULATION

Bayesian approaches to the valuation of information have been available for some time [11–14] but have only recently been applied to the economic evaluation of health care technologies [15–17]. Information is valuable because it reduces the expected costs of uncertainty surrounding a clinical decision. The expected costs of uncertainty is determined by the probability that a treatment decision based on existing information will be wrong and the consequences if the wrong decision is made. The expected costs of uncertainty can also be interpreted as the expected value of perfect information (EVPI) since perfect information (an infinite sample) can eliminate the possibility of making the wrong decision. It is also the maxi-

mum a decision-maker should be willing to pay for additional evidence to inform this decision in the future. If the EVPI exceeds the expected costs of additional research then it is potentially cost-effective to demand more information to substantiate a claim.

The EVPI is determined by the prior mean net benefit of the new technology, the amount of prior information available, and the value placed on opportunity losses when they occur. Information is non rival so the EVPI is also determined by the size of the patient population who could benefit from the new technology. Clearly the value of information can vary substantially across new technologies with different characteristics. The EVPI can also be established for each uncertain parameter in economic models of health care technologies. This can be used to focus the demands of regulatory authorities on getting more precise estimates of particular variables which may not necessarily require experimental design.

Observing an EVPI greater than the cost of additional research provides only the necessary but not sufficient condition for demanding more experimental information to substantiate a claim. It is necessary to estimate the benefits of sampling, or the expected value of sample information (EVSI) for the patient population, and the cost of sample information including the additional treatment and reporting cost. The difference between the EVSI and sampling cost is the expected net benefits of sampling (ENBS) or the societal payoff to proposed research. An estimate of the ENBS for every feasible allocation of each sample size is required to identify the optimal allocation of trial entrants (where ENBS reaches a maximum for a given sample size). The optimal sample size for the trial is where ENBS reaches a maximum (given optimal sample allocation). If the maximum ENBS is greater than the fixed costs of the research then it will be efficient to demand additional experimental evidence at this technically efficient scale and design.

The characteristics of four stylized numerical examples are detailed in Table 1. These examples can represent different technologies or the same technology in different circumstances where: the difference between Example 1 and 2 is that the marginal costs of sampling for the experimental and control group is higher in Example 1; the difference between Example 2 and 3 is that prior variance is greater in Example 3 (there is less prior information available and more uncertainty); and the difference between Example 3 and 4 is that the population that can benefit from additional information is higher in Example 4. The EVPI, ENBS and optimal sample size for each example are reported in Table 2. These examples demonstrate that the value of information and optimal sample size is determined by the characteristics of new technologies and the monetary valuation of health outcome (1/g).

Clearly the efficient scale and design of experimental research will differ substantially across technologies with different characteristics. Indeed in some circumstances it will not be efficient to acquire experimental information because the fixed costs of research exceed the maximum ENBS (see Example 1 in Table 2). In these cases a claim can be substantiated on prior evidence alone. In other circumstances very large clinical trials, far in excess of the current regulatory demands, will be efficient. What distinguishes the classical/frequentist approach from the decision theoretic is that in the former a decision rule and sample size are selected to achieve a predetermined α and β while the latter solves for a decision rule and sample size which meets an explicit objective (maximize health gain for a given budget).

CONCLUSION

Regulatory authorities should demand more evidence for substantiation of a claim if the expected benefits exceed the expected costs of additional information. Efficient regulation would demand more information for some new technologies as compared to others and require different amounts of information for the same technology in different circumstances. The appropriate role of regulatory authorities should be to police the prior information which is explicitly used in this type of analysis and implicitly used in the classical approach (the US EPA already plays a similar role in policing exposure and potency assumptions in models of environmental hazards). Information is non rival and a public good so regulatory authorities must also ensure that the disincentive of being the first to develop a new technology where there is little prior information and a large eligible population is mitigated by flexible patent life. This flexibility has already being used by the FDA

Table 1. Characteristics of stylized examples (different technologies or the same technology in different circumstances)

	Example 1: good prior information; high marginal sampling cost; small patient population	Example 2: good prior information; low marginal sampling cost; small patient population	Example 3: poor prior information; low marginal sampling cost; small patient population	Example 4: poor prior information; low marginal sampling cost; large patient population
Incremental cost[a]				
Prior mean	\$5000	\$5000	\$5000	\$5000
Variance	\$12 000	\$12 000	\$12 000	\$12 000
Prior variance	\$14	\$14	\$40	\$40
Incremental utility[a]				
Prior mean	0.2	0.2	0.2	0.2
Variance	36	36	36	36
Prior variance	0.045	0.045	0.12	0.12
Incremental CER	\$25 000	\$25 000	\$25 000	\$25 000
Patient population p.a.[b]	1000	1000	1000	5000
Marginal cost of sampling[c]				
Experimental arm	\$7000	\$6000	\$6000	\$6000
Control arm	\$2000	\$1000	\$1000	\$1000

[a] For simplicity the covariance between incremental costs and utilities is assumed to be zero.
[b] An effective life of 5 years is assumed for this new technology and the patient population is discounted at 6%.
[c] Marginal sampling costs include incremental costs for the experimental arm and marginal reporting costs for both experimental and control.

Table 2. EVPI, ENBS, optimal sample size and sample allocation[a]

	Example 1: good prior information; high marginal sampling cost; small patient population	Example 2: good prior information; low marginal sampling cost; small patient population	Example 3: poor prior information; low marginal sampling cost; small patient population	Example 4: poor prior information; low marginal sampling cost; large patient population
EVPI				
$1/g$ [b] = \$30,000	\$9 242 531	\$9 242 531	\$16 365 054	\$81 825 268
$1/g$ = \$50,000	\$9 791 624	\$9 791 624	\$20 967 597	\$104 837 987
Optimal sample size				
$1/g$ = \$30 000	398	508	580	1754
$1/g$ = \$50 000	0	609	744	2129
Allocation to experimental				
$1/g$ = \$30 000	145	171	220	686
$1/g$ = \$50 000	0	201	290	856
Maximum ENBS				
$1/g$ = \$30 000	\$1 205 135	\$1 642 525	\$7 602 926	\$58 154 874
$1/g$ = \$50 000	\$0	\$303 118	\$8 856 924	\$72 388 088

[a] The analysis of the value of information and optimal sample allocation uses methods which have been outlined in Claxton [15].
[b] $1/g$ = monetary valuation of health outcome or shadow price of the budget constraint (slope of the loss function).

to encourage pediatric clinical trials of new and approved drugs [9]. The consequences of the existing arbitrary regulation will be distorted research and development priorities, inappropriate approval decisions and less than optimal flow of pharmacoeconomic information, all of which will have tangible costs in terms of health gains forgone. These issues seem to be recognized by regulatory agencies and Bayesian decision theory provides the practical tools to implement a more rational approach to regulation.

ACKNOWLEDGEMENTS

I would like to thank two anonymous referees for their comments on previous drafts. This paper has benefited greatly from discussions with Milton Weinstein, Peter Neumann, and Mark Berger. I would like to acknowledge the support provided by the Harkness Fellowships of the Commonwealth Fund of New York and the Harvard Center for Risk Analysis.

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