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Brief Report

How Uncertainty Matters Under Risk Neutrality

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ABSTRACT

It is typical in cost-effectiveness analysis to invoke a normative decision-making framework that assumes, as a starting point, that "a quality-adjusted life-year (QALY) is a QALY is a QALY." The implication of this assumption is that the decision maker is risk neutral and that expected values could be considered sufficiently informative for a given "approve or reject" decision. Nevertheless, it seems intuitive that less uncertainty should be desirable and this has led some to incorporate "real" risk aversion (RA) into cost-effectiveness analysis.

We illustrate in this article that RA is not always necessary to justify choosing more over less certain options. We show that for a risk neutral decision maker, greater uncertainty can make the approval of technology less likely in the presence of (1) model nonlinearities, (2) nonlinear opportunity costs, and (3) irreversible costs. We call these cases of "apparent" RA.

Incorporating explicit risk preferences into decision making can be challenging; nevertheless, as we show here, it is not necessary to justify caring about uncertainty in approval decisions.

Keywords: decision making, risk aversion, risk preference, uncertainty.

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Introduction

In healthcare decision making, there are many reasons that patients and decision makers wish to limit or avoid uncertainty in outcomes. This uncertainty can have a variety of causes such as: uncertainty about the average treatment effect of an intervention, variability in individual patient outcomes, or structural uncertainty inherent in decision modeling.[1,2] Nevertheless, it is typical in cost-effectiveness analysis to invoke a normative social decision-making framework that assumes "a quality-adjusted life-year (QALY) is a QALY is a QALY."[3] The implication of this assumption is that the decision maker is risk neutral (RN) and that expected values can be considered sufficiently informative for a given "approve or reject" decision.[4] Nevertheless, it seems intuitive that less uncertainty should be desirable and there is an extensive toolkit for presenting uncertainty, for example, cost-effectiveness acceptability curves and cost-effectiveness planes.

Risk aversion (RA) is a concept from economics that is often invoked to explain why uncertainty matters. The textbook formulation of RA requires diminishing marginal utility associated with an outcome of interest (As identified by an anonymous reviewer diminishing marginal utility struggles to explain RA in empirical studies, see Rabin[5]). An RA actor will prefer outcomes with low uncertainty, even if the expected outcome of the more uncertain choice is the same or of higher value than the more certain outcome.[6]

Health technology assessment commonly takes the objective of maximizing health (ie, QALYs) given a constrained budget. This maximization entails no consideration of diminishing social utility of population-level QALYs and thus implies RN.

This brief report describes scenarios in which we care about additional uncertainty even under RN. This shows that greater uncertainty can reduce the favorability of approving a new technology even if the decision maker is RN. This we term "apparent RA." The aim is to clarify the normative value frameworks that underpin decision making under uncertainty and illustrate how RA can be sufficient but is not a necessary condition for decision makers to choose more certain treatment options.

Decision Making Under RN

We assume a centrally allocated fixed budget for healthcare, funded through general taxation, such as that which exists in the United Kingdom. Correspondingly, we take the social decision maker approach in which decisions are made on behalf of populations by a socially mandated decision maker. Other approaches to incorporating risk preference into healthcare decision making analyze different healthcare systems and therefore have appropriately conceptualized the decision problem differently to the present article.[7,8] Many healthcare systems, even those with significant market aspects (such as the United States), will have some component of centralized allocation and so this article may provide a useful starting point for wider discussions. Note that we assume population-level decision making and so we do not consider the preferences individuals may have to reduce variability in their own outcomes.

As is standard in health technology assessment, this article considers decision making about a single specific project. It does not consider portfolios of interventions.[9,10]

Population-Level Decision Making

Consistent with the objective of maximizing population-level health subject to a fixed budget for healthcare, social decision makers are interested in the incremental net benefit offered by a new intervention that represents the health gains for patients less the opportunity cost.[11]

Suppose a new intervention is estimated to impose an incremental cost of ΔC and generate an incremental health gain of ΔH relative to the next best comparator. These variables are calculated on the basis of a vector of uncertain inputs, θ. The opportunity cost of the new intervention reflects the health consequences of displaced activities from within the existing budget.[12] This can be calculated by dividing the incremental cost by the cost per unit of health produced by the healthcare system at the margin (k), which itself may vary with the scale of the incremental cost imposed ($k(\Delta C)$).[13] The resulting incremental net benefit of the new intervention can be written as follows.

$$INB(\Delta H, \Delta C, k, \theta) = \Delta H(\theta) - \frac{\Delta C(\theta)}{k(\Delta C(\theta))} \tag{1}$$

Rearranging this equation (assume $\Delta H, \Delta C < 0$) gives the familiar result that an incremental net benefit will be positive if the incremental cost-effectiveness ratio ($ICER$) is less than a cost-effectiveness threshold (CET) that reflects the cost per unit of health produced by the healthcare system at the margin.

$$ICER(\Delta H, \Delta C, \theta) = \frac{\Delta C(\theta)}{\Delta H(\theta)} \tag{2a}$$

$$CET(k, \Delta C, \theta) = k(\Delta C(\theta)) \tag{2b}$$

$$INB(\Delta H, \Delta C, k, \theta) < 0 \text{ if } \frac{\Delta C(\theta)}{\Delta H(\theta)} < k(\Delta C(\theta)) \tag{2c}$$

How Uncertainty Matters Under RN

Below we discuss some scenarios in which apparent RA arises and we use this to clarify the ways in which uncertainty matters to RN decision makers.

Nonlinear Decision Models

Decision-analytic models are used to calculate $ICER(\Delta H, \Delta C, \theta)$. Commonly they incorporate a degree of nonlinearity in relating inputs to estimated model outputs. The result is that there will be a discrepancy between the expected model outputs and the model outputs calculated at the expectation of the inputs.

$$E(ICER(\Delta H, \Delta C, \theta)) \neq ICER(\Delta H, \Delta C, E(\theta)) \tag{3}$$

For this reason, it is considered best practice to calculate the ICER by averaging over probabilistic sensitivity analysis simulations (“probabilistic ICER”), rather than giving the ICER at average values of θ (“deterministic ICER”), when the model is nonlinear.[1]

In general, ICERs are thought to be concave in θ meaning that the deterministic ICER is lower than the probabilistic ICER with the magnitude of the difference increasing with uncertainty in θ.[14] Thus, calculation of the ICER is itself a function of the uncertainty associated with θ. For this reason, greater uncertainty makes it more unlikely that the new intervention generates a positive incremental net benefit. Therefore, the social decision maker may be expected to demonstrate apparent RA even though they have not deviated from a normative value framework built around health maximization.

Nonlinearity in Opportunity Costs

Although there is an understanding of the importance of incorporating uncertainty in the calculation of ICERs because of nonlinearity, a less appreciated implication of our conceptual framework is that health opportunity costs may be nonlinear in incremental costs. This nonlinearity will pertain unless cost per unit of health produced by the healthcare system at the margin is considered to be constant with respect to the scale of the incremental cost imposed. Interestingly, this is inconsistent with diminishing marginal health returns to expenditure in the health production function, which is practically universally assumed in theoretical and empirical work.[15,16] Incorporating diminishing marginal returns results in a cost per unit of health produced by the healthcare system at the margin that is convex; that is, greater uncertainty in the inputs reduces its expected value.

$$E(k(\Delta C(\theta))) < k(\Delta C(E(\theta))) \tag{4}$$

Convexity in the cost per unit of health produced by the healthcare system at the margin in turn implies that health opportunity costs are concave in θ, which means that a technology with a more uncertain costs has a higher health opportunity cost. The result is that an RN social decision maker concerned with maximizing health would be less likely to approve the new more uncertain technology.

Irrecoverable Costs and the Possibility of Collecting Additional Evidence

Value of information methods can be used to provide decision makers with estimates of the health benefits of resolving decision uncertainty. These methods are well established in the field of health economics and have been described and applied extensively.[4,17,18] Although these methods can accommodate the assumption of RA, it is not a necessary condition for reducing uncertainty to provide positive health benefits.[7,19]

Currently for many decision-making bodies, the only decision options available are to approve or reject a given technology. Decisions about further research tend to be made by separate entities. Even decision makers without commissioning powers face opportunity losses from uncertainty in decision making. This is because approving technologies unconditionally remove the incentive for further research.[20] Therefore, an RN decision maker may reject a cost-effective technology because of excess uncertainty to balance the benefits of early approval for current patients against the opportunity costs of a more uncertain evidence base borne by future patients.

Further to this, there now exist frameworks that allow decision makers to move beyond simple “accept or reject” decisions to take account of the possibility of gaining further information.[21,22] Thus, the decision options extend to Only in Research in which a technology is only to be used in research and is not approved for widespread use, and Approval With Research in which a technology is approved for widespread use and simultaneously investigated in research.

An important consideration when making simultaneous approval and research decisions is the existence of irrecoverable costs. Irrecoverable costs are costs that are incurred by approval of a technology that cannot be clawed back, for example, upfront capital investment.[17,21] Irrecoverable costs affect the approval decision because even if the new treatment looks superior in expectation it may still be optimal to issue an Only in Research decision to resolve uncertainty before incurring large irrecoverable costs.[21]

Even for an RN decision maker, reducing decision uncertainty will make approval more likely because the value of further research will be reduced, which makes an immediate approval decision (without research) more likely.

Discussion

In this article, we have outlined 3 scenarios that illustrate how RN decision maker cares about uncertainty. In summary, RN decision makers must account for uncertainty, in nonlinear decision models to get appropriate estimates of costs and health outcomes, when there are nonlinear opportunity costs to gain an appropriate estimate of the health consequences of changes in resources, and when there is the possibility of further research, so that either incentive, a preserved or potentially avoidable irrecoverable cost, is avoided.

As stated, the examples presented here may not translate directly to different health systems that require individuals to make personal decisions about purchasing insurance to cover individual risk of illness. Nevertheless, the authors expect that there will still exist instances of apparent RA in this context. The aim of this article is to illustrate the ways in which an RN decision maker can care about uncertainty.

In this article, we took health maximization as the objective. Implicitly this means that our analysis did not distinguish between ΔH and health opportunity costs imposed because of any increased costs $\left(\frac{\Delta C(\theta)}{k}\right)$. This is a consequence of the collective fixed budget in which all consequences are ultimately in terms of population health. Therefore, this objective also means that it is not coherent to allow different risk preferences for costs compared with health outcomes.

We are not arguing for or against the existence of RA in this article. In each case of apparent RA, a social decision maker could also have RA preferences. Any social welfare function will be rightfully contested. As analysts, we see our role as increasing the transparency and accountability of decision making. Furthermore, for a decision maker tasked with making decisions on behalf of populations, we think that there are difficulties measuring such preferences. This is because risk preferences concerning an individual's own health are unlikely to map directly to preferences concerning population health in the abstract. Health valuation studies, such as those used to construct the QALY, should account for risk preferences. Nevertheless, these individual risk preferences are distinct from preferences at the social level.

Earlier we discussed the possibility of collecting evidence to reduce uncertainty. Because all uncertainty can never be eliminated, even under RN there remains a question about the degree of tolerance for uncertainty. In a value of information framework, information should be gathered until the costs of collecting information outweigh the benefits. Therefore, this tolerance will differ across clinical decisions given that the costs and benefits of collecting further information will differ.

We only considered 3 cases to illustrate how uncertainty matters to an RN decision maker; nevertheless, there are likely to be more. Other areas of consideration that may also produce instances of apparent RA are linear programming problems,[23] discounting, equity considerations, and dealing with structural uncertainty.

It is also worth noting that, in addition to apparent RA, decision makers may exhibit apparent risk loving preferences in their decision making. A recent example is arguably the Innovative Medicines Fund in the UK, which fast-tracks highly uncertain new drugs for patients with unmet need.[24] It is not clear how this approach can be rationalized under the assumption of an RN population-level decision maker. Nevertheless, it is somewhat consistent with frameworks based on individuals under RA where severely ill patients may choose highly uncertain treatments when the returns are positively skewed.[8]

By exploring these instances and unbundling the concept of risk preference, we can gain clarity on our model of social decision making that can facilitate transparent and accountable decision making.

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