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HEALTH POLICY ANALYSIS

The Impact of Decision Makers' Constraints on the Outcome of Value of Information Analysis

Hendrik Koffijberg, PhD[1,2], *Saskia Knies, PhD*[3], *Mart P. Janssen, PhD*[2,4,*]

[1]*Department of Health Technology and Services Research, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands;* [2]*Department of Medical Technology Assessment, Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht, The Netherlands;* [3]*National Health Care Institute (Zorginstituut Nederland), Diemen, The Netherlands;* [4]*Transfusion Technology Assessment Department, Sanquin Research, Amsterdam, The Netherlands*

ABSTRACT

Background: When proven effective, decision making regarding reimbursement of new health technology typically involves ethical, social, legal, and health economic aspects and constraints. Nevertheless, when applying standard value of information (VOI) analysis, the value of collecting additional evidence is typically estimated assuming that only cost-effectiveness outcomes guide such decisions. **Objectives:** To illustrate how decision makers' constraints can be incorporated into VOI analyses and how these may influence VOI outcomes. **Methods:** A simulation study was performed to estimate the cost-effectiveness of a new hypothetical technology compared with usual care. Constraints were defined for the new technology on 1) the maximum acceptable rate of complications and 2) the maximum acceptable additional budget. The expected value of perfect information (EVPI) for the new technology was estimated in various scenarios, both with and without incorporating these constraints. **Results:** For a willingness-to-pay threshold of €20,000 per quality-adjusted life-year, the probability that the new technology was cost-effective equaled 57%, with an EVPI of €1868 per patient. Applying the complication rate constraint reduced the EVPI to €1137. Similarly, the EVPI reduced to €770 when applying the budget constraint. Applying both constraints simultaneously further reduced the EVPI to €318. **Conclusions:** When decision makers explicitly apply additional constraints, beyond a willingness-to-pay threshold, to reimbursement decisions, these constraints can and should be incorporated into VOI analysis as well, because they may influence VOI outcomes. This requires continuous interaction between VOI analysts and decision makers and is expected to improve both the relevance and the acceptance of VOI outcomes.

Keywords: decision making, multiple constraints, reimbursement, research prioritization, value of information.

Introduction

After effectiveness has been demonstrated, decisions on reimbursement of new health technologies in most Western European countries are based on, among others, ethical, juridical, social, and health economic considerations. Examples of such considerations are maximum budget impact, maximum complication rates (CRs), minimum overall health benefits, and health equity. Currently, the interest in the application of health technology assessment with explicit and transparent incorporation of multiple constraints or decision criteria is increasing [1–4]. Methods for explicating and valuating constraints have been developed [5–7], and various approaches to decision making on the basis of multiple constraints exist [8–10].

When decision makers consider new technology (NT) they typically have more options than immediately approving or rejecting. For example, a decision maker might consider supporting or reimbursing an NT "only in research" or "approved with research" [11,12]. Such decisions can be informed by evaluating the current uncertainty surrounding the health economic results, and determining the value of reducing that uncertainty, to improve decision making in a value of information (VOI) analysis [13–15]. Here, it is recognized that the collection of additional evidence to enhance the decision outcome may be affected by the reimbursement decision itself. For example, full unconditional reimbursement of an NT may make it hard to collect new evidence on current usual care (UC) if the NT would rapidly replace current care in clinical practice. This challenge can be

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* *Address correspondence to:* Mart P. Janssen, Department of Health Technology Assessment, Julius Center for Health Sciences and Primary Care, UMC Utrecht, Huispostnummer Str. 6.131, P.O. Box 85500, Utrecht 3508 GA, The Netherlands.

E-mail: m.p.janssen@umcutrecht.nl.

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addressed by separately assessing the expected impact of “only in research” and “approved with research” decisions, as alternatives to an “approve or reject” decision, and determining the optimal decision from this set. Nevertheless, constraints arising from any of the considerations mentioned are typically not included in the VOI analysis and are also not incorporated into this wider set of possible decisions. In other words, VOI outcomes are mostly derived considering that policy decisions are determined by cost-effectiveness outcomes only.

In this article we illustrate how explicit additional constraints on the acceptability of new health technology may be incorporated into VOI analysis, and how this may affect VOI outcomes.

Methods

We assessed the impact of two plausible constraints on the reimbursement decision regarding a new hypothetical health technology in a simulation study. In this study we compare costs and effects of the NT with UC.

Outcomes of the NT and UC

We evaluated the cost-effectiveness of an NT compared with UC. Mean costs were set to €8000 ± 1000 for UC and €10,000 ± 2000 for NT. Mean effects were expressed in quality-adjusted life-years (QALYs) and set to 0.45 ± 0.30 for UC and 0.60 ± 0.20 for NT. In addition, the CRs for UC and the NT were set to 2.75% (0.15%) and 2.75% (0.55%), respectively. Here, the impact of complications from use of the NT, or UC, was assumed to be included in the respective cost and effect outcomes. Correlations were defined between the costs and effects and between the CRs and effects (separately for NT and UC) as well as between the effects of NT and UC. The Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.011 contain a table with an overview of all simulation parameters, including the ensuing correlations between all parameters and the source code used for the simulations. Uncertainty in costs, effects, and risk of CRs was simulated using multivariate normal distributions with mean and SD as indicated (1,000,000 samples).

Description of the Constraints

We applied a cost-effectiveness threshold of €20,000 per QALY gained as health economic constraint, a threshold that is commonly referred to in the Netherlands [16]. In addition, we defined a constraint regarding the maximum acceptable CRs. This constraint was represented by an absolute threshold of 3% CR for the NT. This threshold could represent advice from medical professionals and patient organizations regarding the maximum clinically acceptable CRs. If evidence would suggest that the expected CR for the NT exceeds this threshold, it would not be considered an acceptable alternative to UC. This would apply regardless of 1) the cost-effectiveness of the NT and 2) the CR of UC (which have been deemed acceptable in the past, even though this rate may exceed the CR threshold currently set for the NT). Finally, we also defined a constraint on the maximum *additional* costs incurred by NT compared with UC. Here, the threshold was set to €2500. Combined with, for example, a potential target population of 1000 individuals eligible to receive the NT, this would correspond to a maximum additional budget of €2,500,000. New technologies exceeding such a budget increase require further and more detailed analysis in the Netherlands.

Calculating the VOI Outcomes and Decision Options

To derive the expected VOI we started by calculating the net monetary benefit (NMB) for both alternatives. Next, the NMB for both alternatives was calculated per sample separately. The current best option was determined by selecting the alternative with the highest expected NMB. The expected value of perfect information (EVPI) was determined by first selecting the alternative with the highest expected NMB, separately for each sample, and then subtracting the expected NMB of the current best option from the expected NMB of selecting the best option per sample [17,18].

Calculating the VOI When Constraints Apply

In case constraints apply, a decision maker might still prefer UC over NT even when the *expected* CR or *expected* additional costs for NT do not exceed the constraint threshold(s), but the *risk* of exceeding a threshold(s) is deemed to be substantial. Such a “risk-averse” attitude would render UC to remain the preferred option despite potential benefits of NT. In our example we presumed that a risk-averse decision maker would not prefer NT in case the risk of exceeding constraint thresholds would be more than 30%. Note that this is an arbitrary threshold value.

For the calculation of the EVPI in our example, a Monte-Carlo simulation was performed in which 1,000,000 samples were drawn. Constraints were applied for CRs and the maximum additional costs for NT. From these samples the expected NMB and the threshold exceedance probabilities were calculated for both NT and UC, and the best option was determined. The best option was again determined but now separately for each sample. Finally, the EVPI was calculated from the difference in NMB of the best option across all samples and the expected NMB of the best options per sample. To calculate the EVPI while applying constraints, the following six steps were taken; Table 1 provides an illustration of these steps performed for five random samples.

1. Calculate the expected NMB for NT and UC and the risk of exceeding the constraint threshold.
2. Determine the best option, that is, the alternative with the highest NMB that complies with the applicable constraints and with an acceptable risk of exceeding these constraints.
3. Determine for each sample whether NT complies with specified constraint(s).
4. For each sample define the highest *acceptable* NMB as:
   a. the NMB of UC in case of noncompliance of NT with the applicable constraint(s);
   b. the highest NMB of UC and NT in case of compliance of NT with the applicable constraint(s).
5. Calculate the expected highest acceptable NMB over all samples.
6. Subtract the expected NMB of the current best option (step 2) from the expected highest acceptable NMB (step 5).

Note that if multiple constraints are applied, all constraints have to be met by the NT in step 4a of the analysis before its NMB is even compared with the NMB of UC. Also, in case the expected NMB of NT is higher than that of UC the EVPI for the risk-averse decision maker will increase by the difference between the expected NMB of NT and that of UC because this is the benefit the additional information provides by opening up the possibility of actually implementing NT.

All calculations were performed using the statistical package R version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria) [19].

Results

Figure 1 shows the incremental cost-effectiveness plane for NT compared with UC. The expected difference in health outcomes equals 0.15 QALYs; the difference in costs is expected to be €2000. The NMB of UC equals €1000 per patient, whereas the NMB of NT equals €2000 per patient. Therefore, NT is expected to be preferred over UC, given this cost-effectiveness threshold.

Table 1 – Examples of individual sample outcomes and associated decision outcomes.

Sample	Usual care				New technology[*]			
	Effect (QALYs)	Cost (€)	CR (%)	NMB (€)	Effect (QALYs)	Cost (€)	CR (%)	NMB (€)
1	0.40	7000	2.65	1000	0.45	5000	1.10	4000
2	0.05	−1000	2.60	2000	0.45	**3000**	2.30	6000
3	0.45	10,000	2.70	−1000	0.70	12,000	**3.20**	2000
4	0.10	1500	3.05	500	0.30	1500	2.90	4500
5	0.35	2000	2.90	5000	0.10	**5000**	**5.10**	−3000
Expected outcome	0.27	3900	2.78	1500	0.40	5300	2.92	2700

Sample	Selected best option				Sample	NMB (€) of selected best option			
	No constraints[†]	CR constraint[‡]	Budget constraint[§]	CR and budget constraints[‡,§]		No constraints[†]	CR constraint[‡]	Budget constraint[§]	CR and budget constraints[‡,§]
1	NT	NT	NT	NT	1	4000	4000	4000	4000
2	NT	NT	UC	UC	2	6000	6000	2000	2000
3	NT	UC	NT	UC	3	2000	−1000	2000	−1000
4	NT	NT	NT	NT	4	4500	4500	4500	4500
5	UC	UC	UC	UC	5	5000	5000	5000	5000
Probability that NT is the best option	80%	60%	60%	40%	Mean value	4300	3700	3500	2900
Selection based on expected NMB outcomes	NT	NT	NT	NT	EVPI[‖] (€)	4300–2700 = 1600	3700–2700 = 1000	3500–2700 = 800	2900–2700 = 200
Selection based on expected outcomes, without unacceptable risk of noncompliance of the NT	NT	UC	UC	UC	EVPI[¶] (€)	4300–2700 = 1600	3700–1500 = 2200	3500–1500 = 2000	2900–1500 = 1400

Note. In this table for five potential outcomes (samples) for UC and NT the associated costs, health effects, CRs, and NMBs are given, as well as the expected outcomes for these five samples. In the second part of the table the selected best options and the associated NMBs are shown for each of the four scenarios considered: no constraints, CR constraint, budget constraint, and budget and CR constraints. In addition, the EVPI is calculated on the basis of the best option given the expected outcomes (the alternative with the highest NMB, NT for all scenarios in this case, indicated by EVPI[‖]), and the EVPI for a risk-averse decision maker (UC whenever a constraint applies, indicated by EVPI[¶]). Note that all boldfaced numbers in the table indicate potential exceedance of constraints.

CET, cost-effectiveness threshold; CR, complication rate; EVPI, expected value of perfect information; NMB, net monetary benefit; NT, new technology; QALY, quality-adjusted life-year; UC, usual care.

[*] On the basis of current evidence, NT is the best option; the corresponding NMB is €2700.

[†] Only a CET of €20,000 per QALY is applied.

[‡] CR constraint: CR < 3.0%.

[§] Budget constraint: additional cost of NT less than cost of UC + €2500.

[‖] The EVPI is calculated as the average NMB over all selected best option samples minus the NMB of the alternative with the highest average NMB.

[¶] As EVPI[‖] but without risk of noncompliance with the applicable constraint(s).

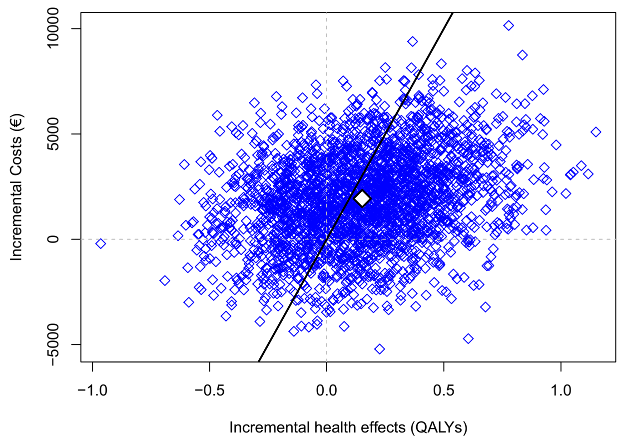

Fig. 1 – The incremental costs and health effects of NT as compared with UC. A cost-effectiveness threshold of €20,000 per QALY is indicated. NT is expected to improve health outcomes at increased but acceptable costs (the estimated mean is less than the cost-effectiveness threshold). NT, new technology; QALY, quality-adjusted life-year; UC, usual care.

Current evidence, however, indicates that it is rather uncertain whether NT indeed is more cost-effective than UC (Fig. 1). There is a 43% probability that UC would still be preferred over NT.

In our analysis CRs are also considered, separate from but related to health effects (more details are provided in Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.011). Figure 2A shows the distribution of outcomes for both alternatives in terms of their CRs and health effects. From this figure it is clear that NT is expected to improve health outcomes as compared with UC, but it also has a substantially higher risk of exceeding the CR threshold. Note that UC has, albeit very small, a risk of exceeding this threshold as well. For both alternatives there is a similar negative correlation between the CRs and the provided health effects (see Appendix Table 1 in Supplemental Materials).

Although current evidence suggests that selecting NT would yield an NMB of €2006, selecting the best option per sample would improve decision making and would yield an NMB of €3874 when ignoring any constraints. Therefore, the standard EVPI per patient is estimated to be €1868 (Table 2, row 2). When calculating the EVPI while applying the CR constraint, UC is selected automatically, irrespective of its costs and health outcomes, for all samples in which NT exceeds the CR threshold. Consequently, NT is selected less frequently and the expected probability of exceeding the CR threshold decreases substantially, as do the expected health outcomes and the expected NMB (Table 2, row 3). The corresponding EVPI therefore becomes €1137, which is a reduction by €730 per patient, a relative decrease of 39%. This selection process is shown in Figure 2B in which the selected (optimal) outcomes are colored and the nonselected are shown in gray. Note that occasionally the UC does exceed the CR threshold but NT is never selected when exceeding the CR threshold.

In case the budget constraint of a limited increase of €2500 is applied, the expected NMB for the optimal decision would reduce to €2776 (Table 2, row 4), with an associated EVPI of €770 per patient. Note that the budget constraint reduces the probability of selecting NT more than the CR constraint. There is an increase in the risk of exceeding the budget constraint (as compared with the situation in which the CR constraint is applied). In Figure 3A the impact of the budget constraint on the selection of optimal outcomes is shown. From this figure it is clear that the outcomes of NT with high costs are not selected (shown in gray) as are the outcomes for UC with limited health effects and relatively high costs.

When both the CR and budget constraints are applied, the NMB of the optimal decision becomes €2324 (Table 2, row 5), with an associated EVPI per patient of €318. Again, NT is selected less often because its preference is now restricted by an unacceptable budget increase as well as an elevated CR, despite having a favorable expected NMB. Note that the budget constraint apparently forces the use of UC also for some less favorable outcomes, which leads to an increased risk of exceeding the CR threshold as compared with the situation in which only the CR constraint is considered. Conversely, the risk of exceeding the cost threshold remains 0 whenever the budget constraint is applied, because this criterion is fully controlled by whether NT is selected. Figure 3B shows the costs and CRs of selected samples. The figure clearly illustrates the restriction on costs and CRs on the selected samples.

Note that similar to the results presented in Table 1, in case of a risk-averse decision maker all EVPI estimates presented in Table 2 (when any constraint applies) would increase with the NMB difference between UC and NT. In this example this difference is equal to €1000.

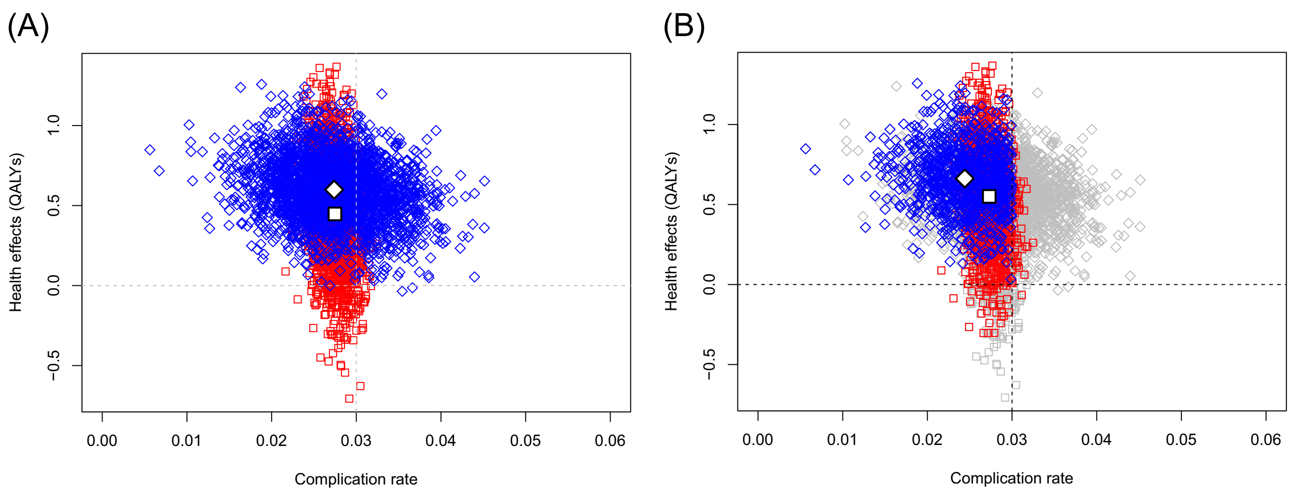

Fig. 2 – (A) The incremental health effects vs. complication rates for UC (□) and NT (◇). (B) The incremental health effects vs. complication rates for optimal selection of UC (□) and NT (◇) when applying the complication rate constraint for NT. Nonoptimal outcomes for UC and NT are shown in gray. NT, new technology; QALY, quality-adjusted life-year; UC, usual care.

Table 2 – Optimal decision outcomes and EVPI estimates given various contraints.

Optimal decision accounting for various constraints applied and information available	Expected NMB (€)	Expected health outcomes (QALYs)	Expected costs (€)	Probability of selecting NT	Average CR	Probability of exceeding CR threshold	Probability of exceeding cost threshold	EVPI (€)*
Average outcomes available only (NT has the highest average NMB)	2006	0.600	9996	1.000	0.027	0.324	0.410	–
Exact outcome information is available—no constraints apply	3874	0.648	9080	0.567	0.027	0.170	0.224	1868
Exact outcome information is available—only a CR constraint applies	3143	0.596	8779	0.408	0.026	0.022	0.161	1137
Exact outcome information is available—only a budget constraint applies	2776	0.547	8167	0.344	0.027	0.123	0.000	770
Exact outcome information is available—both budget and CR constraints apply	2324	0.522	8121	0.247	0.027	0.032	0.000	318

CR, complication rate; EVPI, expected value of perfect information; NMB, net monetary benefit; NT, new technology; QALY, quality-adjusted life-year; UC, usual care.

* Note that the EVPI values are calculated by subtracting the NMB of the optimal decision on the basis of current information (row 1, €2006) from the expected NMB value for the scenario considered. All outcomes are obtained by simulation (simulation code is available in the Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.011). Note that in case the decision maker would have been risk-averse (and had preferred UC instead of NT as the current best option), all EVPI estimates would increase by €1000.

Discussion

In this article we demonstrated that incorporation of explicit additional constraints applied by decision makers beyond the willingness-to-pay (WTP) analysis is feasible, and that doing so affects VOI outcomes. Outcomes in the domain of the performance of the technology, in terms of costs and effects, can be derived and interpreted without knowledge of such additional constraints. Nevertheless, VOI analysis falls in the decision-making domain and therefore requires full knowledge of all relevant constraints.

In theory, standard VOI analyses may also capture additional constraints, but implicitly through adjustment of the WTP threshold. For example, a separate budget impact threshold may not be required if decision makers are willing to and able to lower the WTP threshold accordingly. In practice, however, budget constraints may be applied as a pragmatic solution to the problem of variable health care budgets and separation of budgets across health care domains or type of interventions (which would require varying WTP thresholds and different WTP thresholds per domain). Furthermore, other considerations, such as health equity constraints, may be applied by decision makers recognizing that these would lead to suboptimal health outcomes on population level, which may be very difficult to adjust for in the WTP threshold.

As shown in Figure 4, VOI analyses with incorporation of decision considerations require interaction between the VOI analyst(s) and the decision maker(s). This interaction serves 1) to examine which of the applicable decision considerations, beyond costs and effects, should and can be incorporated into the VOI analysis and 2) to allow interpretation of VOI outcomes by the decision maker(s) while recognizing the extent to which applicable constraints have been incorporated. A first step toward such interaction may be to launch an online VOI platform for a community of decision makers, VOI analysts, medical product developers, and pharmaceutical companies to discuss additional constraints. This could facilitate understanding among all stakeholders regarding the relevance of such constraints, the speed with which they might change, and the feasibility of their incorporation into the VOI analysis. This discussion could result in a consensus set of (fairly) stable, explicit, and manageable additional constraints for incorporation into future VOI analyses.

Currently, VOI analysts may not be aware of all applicable decision considerations [20]. The impact of such unawareness in VOI analysis has been studied in the past [21,22]. Failure to include all relevant considerations may completely overturn the preference landscape, and perhaps counterintuitively either reduce or increase the VOI [21]. It is known that unawareness in the form of unknown constraints in known domains of the decision problem will only reduce VOI outcomes (to a minimum of 0 because the sum of the VOI and the value of awareness

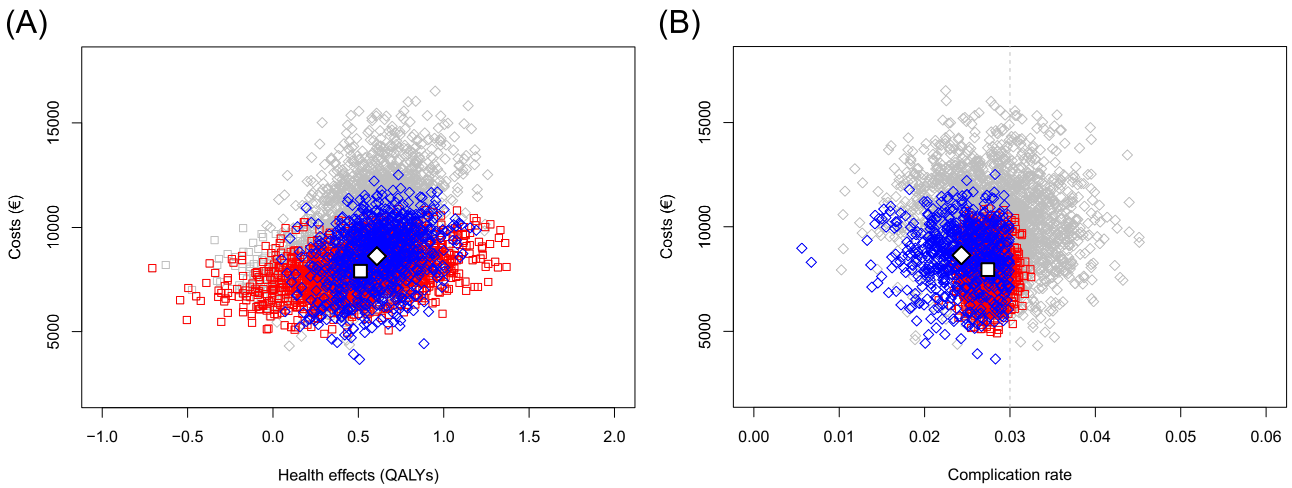

Fig. 3 – (A) Costs and health effects for optimal selection of UC (□) and NT (◇) when applying the budget constraint for NT. (B) Treatment costs vs. complication rates for optimal selection of UC (□) and NT (◇) when applying both complication rate and budget constraints. Nonoptimal outcomes for UC and NT are shown in gray. NT, new technology; QALY, quality-adjusted life-year; UC, usual care.

remains constant) [22]. The impact of constraints in domains not previously considered in the technology domain, however, may result in changes in VOI outcomes of variable size and direction. This implies that explicit incorporation of additional constraints may increase or decrease VOI outcomes, and that these outcomes may even become negative [21].

An example of an increase in VOI is a situation in which the decision uncertainty is low on the basis of comparison of only NMBs (i.e., NT clearly has a higher NMB than UC), whereas decision uncertainty is high when also considering constraints (i.e., NT has substantial chance of not complying with these constraints). In the first situation, the EVPI will be low (NT definitely is the best option). Conversely, in the latter situation, the EVPI will be much higher (UC is the best option, unless NT turns out to nonetheless comply with constraints).

Detailed examples of incorporation of constraints that lead to an increase and a decrease (even to negative values) in EVPI are provided in Appendix Tables 2A and 2B in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.011. Although negative EVPI values may at first appear counterintuitive, or even invalid, they can be easily explained in the context of this study. When optimal strategies are selected on the basis of cost-effectiveness considerations alone, the collection of additional evidence can lead to only potential improvements in cost-effectiveness. Nevertheless, when additional evidence is collected, applying additional constraints may lead to rejection of the option with the highest NMB (when this option turns out to be noncompliant with these constraints) and the selection of compliant alternatives with lower NMB. In this case, collecting additional evidence would result in a lower expected NMB than not collecting this information, and as a result the corresponding EVPI would be negative.

Our analysis has certain limitations. First of all, in practice the change in VOI outcomes from incorporating constraints is likely to be different from the changes shown in our analysis. The impact of incorporating constraints will depend on the extent to which the alternatives considered comply with each of the constraints. For example, if all alternatives are fully compliant with a certain constraint, that constraint will not impact VOI outcomes. Second, in our current assessment constraints were included as fixed threshold values, and exceeding a particular threshold automatically implied that the NT was rejected as a viable alternative. In practice, however, fixed thresholds may not always exist, and weights or

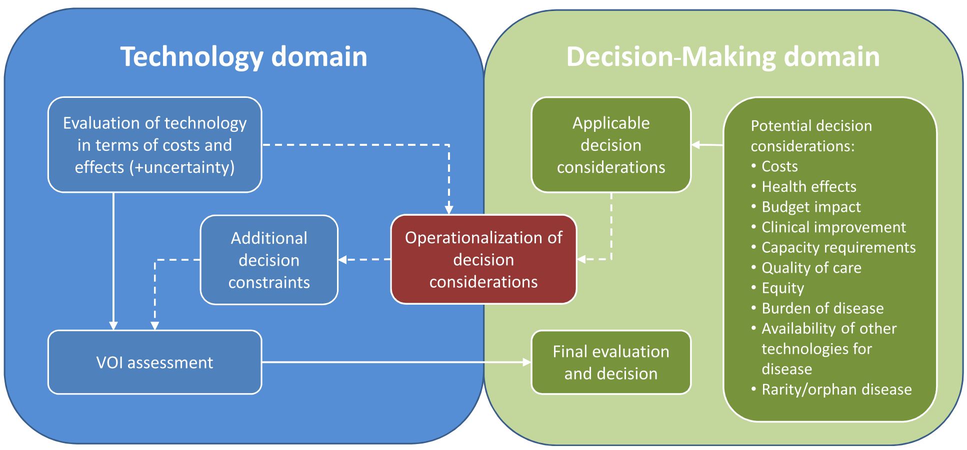

Fig. 4 – Conceptual overview of the technology and decision-making domains and the interaction between VOI analysts and decision makers (red box) and additional steps (dotted lines) required for VOI assessment including constraints. VOI, value of information.

penalties could be given to particular outcomes. For example, alternatives could be penalized by the extent to which they require additional budget compared with UC. Third, in our examples we used an arbitrary threshold of 30% for a risk-averse decision maker to prefer UC over NT. This chosen level of acceptability is not at all generic and will have to be determined by the decision maker for any specific decision and constraint(s) applicable. This again stresses the importance of integration of the technology and decision-making domains. Fourth, our assessment included only two alternatives, one of which (UC) was always considered an acceptable alternative. In practice, more than two constraints may be relevant, and as the number of constraints increases, the likelihood of any alternative being fully compliant rapidly diminishes. Selecting the best option then effectively requires balancing various incompliances that may further complicate decision making. Methods such as the multi-criteria decision analysis have been developed to support such decision processes in a structured and transparent manner [2,20]. Also, we used QALYs as a measure of health effect, whereas other outcome measures may be used instead. Finally, our examples focus on the EVPI as one VOI outcome. More advanced VOI outcomes exist, such as the expected value of partial perfect information, expected value of sample information, attributable expected value of information, and expected net benefit of sampling [23–27]. Constraints can be incorporated explicitly into any such VOI analyses.

Although the relevance of VOI analyses is increasingly recognized, previous research has shown that its implementation in practice is still limited [28]. With improved interaction between VOI analysts and decision makers, the strengths and limitations of VOI analyses may become clearer, and the interpretation of VOI outcomes, and how these match actual decision-making practice, may be enhanced. This study was funded by the Netherlands Organization for Scientific Research.

Conclusions

Incorporating additional, explicit constraints, beyond the standard WTP threshold, into VOI analyses is feasible and desirable if such constraints cannot be reflected by adjusting the WTP threshold accordingly. This requires further integration of the technology and decision-making domains through structured interaction between VOI analysts and decision makers. In fact, in handling decision makers' constraints adequately, the main challenge may not be their explicit incorporation into the VOI analysis, but rather their identification, definition, and acceptance among all stakeholders within a jurisdiction.

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Supplemental Materials

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