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SYSTEMATIC REVIEW

A Systematic and Critical Review of the Evolving Methods and Applications of Value of Information in Academia and Practice

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Abstract
Objective This article provides a systematic and critical review of the evolving methods and applications of value of information (VOI) in academia and practice and discusses where future research needs to be directed.
Methods Published VOI studies were identified by conducting a computerized search on Scopus and ISI Web of Science from 1980 until December 2011 using pre-specified search terms. Only full-text papers that outlined and discussed VOI methods for medical decision making, and studies that applied VOI and explicitly discussed the results with a view to informing healthcare decision makers, were included. The included papers were divided into methodological and applied papers, based on the aim of the study.
Results A total of 118 papers were included of which 50 % ($n = 59$) are methodological. A rapidly accumulating literature base on VOI from 1999 onwards for methodological papers and from 2005 onwards for applied papers is observed. Expected value of sample information (EVSI) is the preferred method of VOI to inform decision making regarding specific future studies, but real-life applications of EVSI remain scarce. Methodological challenges to VOI are numerous and include the high computational demands, dealing with non-linear models and interdependency between parameters, estimations of effective time horizons and patient populations, and structural uncertainties.
Conclusion VOI analysis receives increasing attention in both the methodological and the applied literature bases, but challenges to applying VOI in real-life decision making remain. For many technical and methodological challenges to VOI analytic solutions have been proposed in the literature, including leaner methods for VOI. Further research should also focus on the needs of decision makers regarding VOI.

Key Points for Decision Makers

- Results from value-of-information (VOI) analysis can support the prioritization of further research towards healthcare interventions and, although VOI results are widely available in a growing literature base, it is unclear to what extent these data are used to prioritize further research
- Methodological and computational challenges are considered the major drawback to using VOI in real-life decision making, but analytic solutions for many of these issues are now available
- Future research on VOI should continue to include the development of leaner VOI methods and start to systematically investigate the needs and preferences of decision makers as well as the relative importance of VOI estimates in healthcare and research funding decisions

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1 Introduction

What we know about the value of any particular therapy is bounded by the constraint that gathering information about

the effectiveness of that therapy is costly, both in terms of direct research and patient time costs. Major sponsors of scientific research as well as the device and pharmaceutical industries must weigh the benefits of funding research to obtain information about new and existing medical technologies versus the costs of getting that information, and the alternative of promoting clinical use of those technologies without additional information. The downside of forging ahead without further research is the potential for misjudgement, i.e. making a decision to adopt or not adopt a technology that would not have been made had the true nature of that technology been known.

Value-of-information (VOI) methods have been proposed as a systematic decision-analytic approach for aiding decision makers in assessing whether there is enough evidence to support new therapies, optimally designing research studies and setting research priorities for health technology assessment [1]. Its set of methods for research prioritization is consistent with the methods of cost-effectiveness analysis (CEA) for medical technologies and has a firm theoretical underpinning in statistical decision theory [2, 3].

Some of the earliest publications on decision analysis introduced methods for VOI analyses decades ago [4, 5]. Yet, unlike other economic analytic methods such as CEA, a previous systematic analysis of VOI applications [6] shows the tendency of articles to focus on demonstrating the usefulness of the VOI approach rather than on 'real-time' applications to actual funding decisions. A well-cited example of this in the field of cancer is bone marrow transplantation for women with advanced breast cancer. Decision makers did not have the benefit of a systematic evaluation of the VOI that would be obtained from further trials at the time that the early research was reported. Although legal, political and regulatory issues also influenced the decision to 'adopt' transplantation before clinical trials demonstrated that the procedure offered no survival benefit [138], a formal VOI evaluation might have helped those who advocated for more research before adopting this procedure. Therefore, this paper introduces the concept of VOI in a non-theoretical way and provides a systematic and critical review of the evolving methods and applications of VOI in academia and practice.

2 VOI Analysis

To the extent that decision making between alternative courses of action in healthcare is based on evidence regarding clinical and cost effectiveness and aims to maximize net health benefit, at decision time, any decision maker will (or should) ask himself: Is the current evidence base regarding the clinical and cost effectiveness of this medical technology or treatment sufficiently certain for the decision I'm about to make today? And what are the consequences of an uncertain, and thus potentially wrong, decision? Would postponing the decision to await further evidence increase or decrease the net benefit of healthcare to society?

VOI analysis helps to answer these questions as it can explicitly and quantitatively inform two related decisions, by using specific VOI methods for each [1, 7]. The first decision is whether to adopt a health technology given existing evidence; the second decision is whether more information is required to support this decision in the future [8]. VOI analysis is based on the idea that information is valuable because it reduces the expected costs of uncertainty surrounding a decision. The expected costs of uncertainty are determined by the probability that a decision, based on existing (prior) information, will be wrong and by the consequences of that potentially wrong decision [8]. The expected value of perfect information (EVPI) thus reflects the discrepancy between the current information position and a position of perfect information (no uncertainty). Under the prerequisite that it is calculated globally [9], i.e. over all patients that might be affected by the decision, and allows for a reduction in imperfect information with the strength of the evidence [10], population EVPI can provide a measure of the maximum return of future research, placing an upper limit on the societal costs of it. When VOI analysis is taken one step further onto the expected value of partial perfect information (EVPPI), it informs us for which specific consequences of the technology (e.g. impact on utilities, costs or health status) more information is needed to make a less uncertain decision in the future, again offset by the costs of collecting that further information. Arguably, EVPPI analyses can start directing the future research agenda [8], although Eckermann et al. [1] and others have argued that EVPPI analyses, as well as EVPI analyses for that matter, are neither necessary nor sufficient to inform whether there is sufficient evidence, whether a given research design is worthwhile or even optimal, or which research should be supported. The VOI method of choice to inform such decisions is the expected value of sample information (EVSI), which estimates the expected VOI that could be gathered from a sample of given size n within a particular study design, over a specified time period. Thus, as the EVPI is an upper bound on the returns from further research, the EVSI represents the expected value of new research before conducting a trial of a given sample size [8]. These expected benefits of research can be compared with the expected costs of carrying out that research, i.e. the costs of sampling. The difference between the EVSI and the costs of sampling is the expected net benefit of sampling (ENBS) for a sample size n. If the cost of new research is less than the EVSI, the ENBS from the

information is positive (note that this is regardless of the outcome of the trial) and the trial is worth the expense. The ENBS can be regarded as the societal pay-off to research and can be calculated for a range of samples, sizes and alternative designs [8]. In addition, EVSI estimates should appropriately account for time, as EVSI reduces with time needed for accrual, follow-up and analyses of trials, especially in trials that incur a delay [11].

3 Methods

Scopus and ISI Web of Science were systematically searched from 1980 until December 2011 for peer-reviewed English language papers. Search terms included 'value-of-information analysis', 'expected value of information', 'expected value of perfect information' and 'expected value of sample information'. These terms were searched as stand-alone terms and in combination with the terms 'methods', 'methodology' and 'review'.

Titles and abstracts of all identified references were screened for relevance by two authors (GVDW and LS). Relevant references were retrieved for full-text assessment.

Full-text papers that outlined and discussed VOI methods for medical decision making, and studies that applied VOI and explicitly discussed the VOI estimates in the discussion section of the paper were included. Subsequently, included papers were divided into methodological and applied papers, based on the aim of the study. If the aim of the paper was mainly to demonstrate methodological issues regarding VOI, then the study was considered methodological; if the aim of the paper was to inform a decision about a specific health intervention and VOI was used as a (complementary) decision tool or to prioritize further research, the paper was considered as an applied VOI paper.

Data extraction for both types of papers encompassed: (1) article aim, (2) type of VOI (i.e. EVPI, EVPPI, EVSI or ENBS), and (3) author-described (analytic) challenges of the specific method used. For applied studies, the following additional data were extracted: (4) type of decision to be informed by VOI (i.e. general health policy, specific adoption/reimbursement, coverage with evidence development, future post-market research priorities; or pre-market research and development decisions), (5) application area (i.e. health condition, intervention and comparator), (6) type of decision model used, and (7) type of uncertainty considered (first-, second- or third-order uncertainty). Data extraction was independently performed by four authors (GVDW, KGO, VR and LS). Disagreements were resolved by discussion or referred to the last author (VR). Data were analysed descriptively.

4 Results

As a result of the electronic search, 710 abstracts were identified and reviewed. After removing duplicates and discarding references that were clearly not relevant to VOI in a health economic sense, 164 papers were retrieved for full-text inspection. After excluding the papers that did not describe or discuss the applied VOI methods and results explicitly ($n = 45$), 118 papers were included. In 50 % ($n = 59$) of these studies, VOI methods were the main study subject, whereas in 59 papers VOI was presented as the main or complementary analysis in an applied research paper.

4.1 The Development and Spread of the VOI Literature over Time

Figure 1 gives an overview of the development of the VOI literature base in healthcare, distinguished by methodological and applied papers. Since the study by Thompson [12] first introducing VOI in the field of healthcare, it was not until 1996 that Claxton and Posnett [13] revived this topic. In 1998, Felli and Hazen [14] presented the EVPI as an alternative method for probabilistic sensitivity analysis and in 1999 Claxton [15] proceeded to apply the method to the decision "whether or not to embark on further research", i.e. quantifying the expected value of obtaining more information about the intervention under study. This marked the starting point for a wave of interest in VOI and ultimately to the implementation of the method in the National Institute for Health and Clinical Excellence (NICE)'s technology appraisal procedure. Figure 1 also shows the delay between methodological publications about VOI and its actual application in practice. While from 1999–2000 onwards the methodological research into the topic steadily grew, it was only until 2005 that VOI analysis was becoming more commonly applied in economic evaluations and the number of published case studies has steadily risen since then and catches up with the number of published methodological papers in 2010. The inclusion of VOI analysis in the guidelines for health economic evaluations and in the technology appraisal procedure, as proclaimed by NICE, is likely to be one of the main driving forces behind this development.

As a proxy for the spread of the VOI approach among the medical and health sciences literature, Table 1 in the Appendix shows that the majority of VOI papers have been published in just a few journals, i.e. approximately 60 % of methodological papers have been published in *Medical Decision Making* ($n = 14$) and *Health Economics* ($n = 12$) and approximately 25 % of applied papers appeared in *Health Technology Assessment*. The remaining applied and

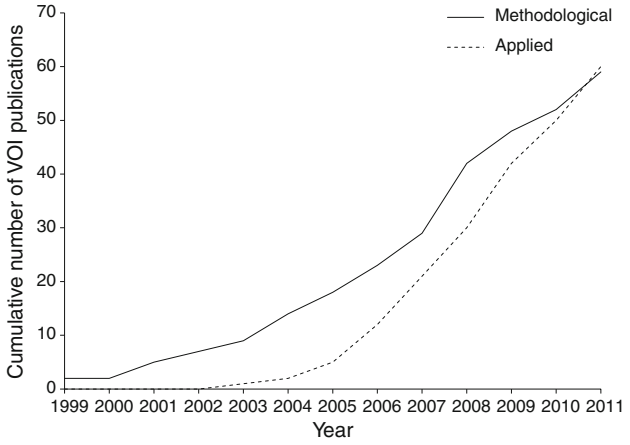

Fig. 1 Development of VOI literature base in healthcare over time. *VOI* value of information

methodological papers were mainly published in *Value in Health* (n = 18, of which 9 were applied papers), *PharmacoEconomics* (n = 11, of which 7 were applied papers) and the *International Journal of Technology Assessment in Health Care* (n = 6, of which 4 were applied papers). Publications in journals other than those with an explicit focus on health economics or health technology assessment are scarce and scattered, with a median of one publication per journal (range 1–3).

4.2 Main Aims of Published VOI Literature

The reported aims of methodological papers can be distinguished into four broad categories. The first category of papers (n = 8) *describes the rationale and key principles* of a Bayesian decision-analytic approach for informing adoption and reimbursement decisions and prioritizing further research [16–23]. After initial publications in this category that were published before the search date of this review [2–5], publication of papers describing the rationale of Bayesian VOI analysis peaks again around 2006, along with the implementation of the VOI pilot project in the UK NHS.

A second category of papers (n = 14) describes the *(potential) role of VOI in regulatory processes* regarding adoption, reimbursement and funding of further research [6, 15, 24–35]. Publication of this type of paper first peaks around 2003–2004 and again between 2006 and 2008.

Another category of papers (n = 24) is concerned with *developing or optimizing mathematical methods* for estimating VOI, specifically the EVPPI and EVSI as these are mathematically the most complex [9, 11, 35–55]. Publication of papers in this category starts to increase steadily from 2004.

A fourth category (n = 13) encompasses a variety of papers setting forth *additional uses or adaptations to VOI* such as VOI to estimating the option value of delay, the value of implementation and average VOI [10, 58–68]. Except for two early publications in 2002 and 2005, the number of papers published in this category peaks in 2008 and remains high after that.

For applied papers, two main categories are distinguished: (1) papers *demonstrating* the application of VOI for a specific treatment; and (2) '*real-life*' applications of VOI. Papers are categorized as 'real-life application' when it was stated in the text that the results of the paper are to inform actual healthcare decision making. Six papers were categorized as VOI demonstration papers [69–74] and concerned the clinical areas of mental health [69], osteoporosis and pressure ulcers [70], age-related macular degeneration [71], intermittent claudication [72], hallux valgus [73] and pharmacogenetic testing for breast cancer [74]. The majority of the applied papers (91 %; n = 54) proclaimed to be real-life applications of VOI [75–128]. The application areas of these papers varied widely, though assessment of cardiac interventions (n = 9) [78, 81, 90–92, 107, 108, 110, 118] and cancer screening or treatment (n = 14) [77, 79, 81, 82, 85, 88, 104, 106, 107, 114, 116, 121, 122, 125] were relatively prevalent among the included papers.

4.3 Types of VOI Presented in the Literature

Except for six methodological papers that deliberate on VOI in general [17, 23, 29, 35, 68, 81], the majority of methods papers consider one or more specific forms of VOI including EVPI (n = 36), EVSI (n = 25), EVPPI (n = 21), and ENBS (n = 16) [see Table 1 in the Appendix]. All applied papers reported EVPI analyses, followed by EVPPI (n = 40), EVSI (n = 6) and ENBS (n = 4) [see Table 1 in the Appendix]. These results indicate that the majority of the application studies estimate the maximal benefits of performing further research, as well as the specific parameters for which further research is most valuable.

4.4 Types of Decisions Informed by VOI

With the results presented in the applied papers, mostly general health policy and research decisions of the type 'should further research into this clinical area or treatment be commissioned and if so, which uncertain parameters should be targeted' are addressed. In 30 studies, specific reimbursement decisions like 'given the current data on cost effectiveness, should treatment X be reimbursed and for whom' were to be informed (see Table 1 in the Appendix). Few studies aimed to support specific decisions regarding pre-market research and development (n = 3) [73, 90, 104].

4.5 Modelling Characteristics

The majority of applied studies (n = 38) used Markov chains to model cost effectiveness and VOI. Decision trees were used as the basis for VOI in 14 studies and three studies combined a Markov model/decision tree approach. One study employed survival curves [90] and another estimated VOI directly from RCT data [96]. In five studies, the type of model used was not stated (see Table 1 in the Appendix) [72, 96, 114, 119, 120]. Parameter (second-order) uncertainty was considered in all applied papers, whereas two applied papers also addressed structural (third-order) uncertainty [70, 71].

4.6 Challenges for VOI

Challenges of VOI as addressed in the applied papers are numerous, but firstly include the high computational demands, particularly of EVPPI, EVSI and ENBS and in the case of non-linear models. Second, it is mentioned that the effective population and the effective lifetime of the technology are often hard to estimate, yet these estimates are likely to have a great impact on the VOI estimates. Third, allowing for correlations between parameters is mentioned as a challenge, as is dealing with structural (third-order) uncertainty (see Table 1 in the Appendix).

The methodological papers also address the high computational demands of VOI analysis in terms of the time needed to run a sufficient amount of simulations. In this regard, Chilcott et al. [26] first note that there is no uniform method concerning the number of Monte Carlo simulations required for convergence to stable VOI results. In 2007, Brennan et al. [43] showed that the use of small Monte Carlo samples and/or shortcut algorithms may indeed lead to biased EVP(P)I estimates. Their empirical investigation of the numbers of Monte Carlo samples suggests that fewer samples on the outer level and more on the inner level could be efficient and that relatively small numbers of samples can sometimes be used. In their case studies, 500 inner loops for each of the 100 outer loop iterations (i.e., 50,000 iterations in total) proved capable of estimating the order of magnitude of EVPPI reasonably well, yet for very accurate calculation or in computationally intensive models, one might use adaptive processes to test for convergence in the EVPPI results, within a predefined threshold. Rojnik and Naversnik [32] successfully solved the conflict between the computationally expensive health economic models and the comprehensive VOI analysis by using a Gaussian process metamodelling technique. This approach, previously suggested by others including Ades and Sutton [19], had a superior performance to the multiple linear regression metamodelling technique and, according to Rojnik and Naversnik [32], "rejects the computational expense as the reason for omission of such analysis". In 2010, Eckermann et al. [1] followed the Occam's razor approach to VOI methods and showed that applying the central limit theorem simplifies analyses to enable easy estimation of EVSI and optimal overall research design. Although more complex VOI methods such as bootstrapping of the EVPPI have potential value in refining overall research design, initial central limit theorem methods that allow the computational burden of more complex methods to be alleviated and can estimate partial EVSI are suggested for use in future research [1].

Estimating the effective population for purposes of EVSI analysis may seem relatively straightforward by considering the prevalence and accumulating the incidence of a given disease over the time horizon of the VOI analysis, minus the number of patients that are proposed to be included in the trial for which the EVSI is calculated. In the initial publications of how to estimate EVSI, the EVSI of a trial is simply the product of the EVSI per patient and the number of patients who can benefit from the decision at the time the information becomes available [15, 39]. However, Eckermann and Willan [11] and Eckermann et al. [61] point out that the number of patients that can potentially benefit from a trial should be reduced, not only by those participating in the trial but also by those outside the trial, over the time until trial evidence is updated, including time for accrual, follow-up and analysis. A method is presented to allow for time in calculating EVSI, which is shown to lead to a reduced EVSI for a specific trial design, increased opportunity costs of trials that are undertaken with a delay and hence a lower likelihood of trialling being optimal [11, 61].

Regarding the estimation of the effective lifetime of the technology, Chilcott et al. [26] and Ades and Sutton [19] note that the expected lifespan of a technology before it is replaced is one of the factors—external to the decision problem—that needs to be addressed while no consensus for doing so exists. Philips et al. [49] have subsequently investigated the impact of the choice of time horizon on the EVPI. What becomes clear from their exploration is that "the current approach of selecting a finite and arbitrary time horizon for EVI (*expected value of information*) calculations is, in essence, an attempt to proxy an uncertain and complex process of future changes" [49]. They also show that "any uncertainty in estimated expected time horizons … will affect the expectation of population EVI because of discounting future costs and benefits" [49]. Furthermore, they show that innovation and price competition leading to the entry of better technologies will ultimately reduce the VOI about existing alternatives, but that attempting to formally model all possible future changes

"would at best be heroic" [49]. To help inform a suitable effective lifetime for purposes of CEA and VOI analysis of drugs, Hoyle [52] found that the historical lifetimes of drugs in England can be modelled as a Weibull distribution with a mean of 57 years and median of 46 years.

Another important challenge within VOI is handling prior parameter correlation [5]. When not appropriately accounted for, prior parameter correlation leads to incorrect posterior calculation of net benefit, including the mean posterior net benefit. It could be argued that when populating a decision model with data derived from unrelated literature sources, the parameters are independent [39]. However, incorporation of all the available data increasingly necessitates the use of computational techniques for combining information on parameters with information on model outputs and other complex functions of several parameters. Such methods inevitably induce parameter correlation [39]. Although using flexible Bayesian Markov Chain Monte Carlo (MCMC) software to carry out complex multiparameter evidence syntheses is likely to support the use of uncorrelated prior parameter structures, it has to be kept in mind that prior parameter correlation is likely to enhance the non-linearity of the relationship between the model outcomes and the input parameters. Coyle and Oakley [47] have demonstrated that for estimating EVPPI in the case of a non-linear model (as may be induced by prior parameter correlation or otherwise) the use of a two-stage Monte Carlo simulation or a quadrature method is advised over a one-stage Monte Carlo or unit normal loss integral method.

The importance of handling structural uncertainty became especially clear following the VOI pilot studies for the UK National Coordinating Centre for Health Technology Assessment (NCCHTA) and the NICE [81]. One of the reasons for this may be that structural assumptions can have less impact on overall cost-effectiveness estimates for alternative strategies (i.e. adoption decisions) than they have on VOI estimates (i.e. research funding decisions), as shown by Bojke et al. [71] and Claxton and Sculpher [81] in their case study on age-related macular disease. Thus, when aiming to implement the VOI framework to inform decision making regarding further research in addition to the 'regular' CEAs that support adoption and reimbursement decisions, the need for handling structural uncertainty became more transparent than before. Although ignoring structural uncertainty will always lead to a biased estimate of the EVPI, it is unknown to what extent it does so in a given VOI analysis of a specific trial, and therefore this hinders decision making between research proposals competing for funding. The need to account for any structural uncertainties appropriately has, for example, been shown by Bojke et al. [71] investigating whether additional research on screening for age-related macular degeneration would be worthwhile. An increase in population EVPI from £6.9 million to £28.9 million was found between two alternative modelling scenarios that differed only as regards their underlying structural assumptions [71]. Fully representing this structural uncertainty and establishing the EVP(P)I or EVSI could be done with a full parameterization of this uncertainty through elicitation of priors from experts and decision makers within an iterative process of analysis [81]. Another method for taking account of structural uncertainty is Bayesian model averaging. Although methods for this are well established in other fields [54, 129, 130], according to a 2009 review by Bojke et al. [131], its use in health technology assessment is limited. Subsequently, a Bayesian approach to model averaging was described and a formula developed for calculating the EVPI in averaged models [54]. When applied to an asthma model, this approach was shown to reduce the standard errors of the incremental net benefit up to ten-fold and the expected loss attaching to decision uncertainty by factors of several hundreds. The method can be extended to calculate EVPPI and EVSI for averaged models [54].

Another factor that challenges the use of VOI in practice is the cost, or 'reversibility', attaching to a decision to change current practice [7, 10, 62, 132]. Palmer and Smith [132] argued that the interest in uncertainty surrounding economic evaluations suggests that "irreversibility" is a major issue in the appraisal of many healthcare technologies. The lower the degree of reversibility of, for example, adopting a new medical treatment, buying a piece of capital equipment or implementing a national screening programme, the higher the cost of reversibility when such would be required in the future. The notion that different new technologies exhibit different degrees of reversibility may be intuitive to decision making in everyday practice, for example investing in a new car is likely to be a more reversible decision than investing in a new house. While reversibility is generally not explicitly considered in health economic evaluation, it can have a major impact on the estimated VOI. Eckermann and Willan [7, 62] demonstrated that "decision makers are generally shown to face joint research and reimbursement decisions, with the optimal choice dependent on costs of reversal as well as opportunity costs of delay and the distribution of prior incremental net monetary benefit" [7]. Option value methods explicitly seek to integrate the uncertainty and irreversibility associated with a technology, into a unifying theory of economic evaluation. As option value

methods offer the decision maker a systematic framework for handling the degree of uncertainty inherent in evidence on the cost effectiveness of a health technology [132], these are likely to be important in health technology assessment. While consistent with all accepted methodologies for the economic evaluation of healthcare interventions, Palmer and Smith [132] argue that the option value approach "may lead to major adjustments to the estimation of a technology's [incremental cost-effectiveness ratio]". One of the main reasons for this is that the passage of time will tend to reveal new estimates for key sources of uncertainty, and that option value methods allow for the option to delay a decision until such information becomes available.

Related to the notion of reversibility costs, as described above, is the notion of 'implementation costs' of new technologies. The implicit assumption within all decision analyses as well as in VOI analyses is that healthcare technologies automatically get implemented into clinical practice [10, 28, 63, 65]. Yet patients and healthcare professionals may not to adhere to guidance, which compromises the efficiency of healthcare provision in terms of the health and resources forgone, and implementation strategies, e.g. education or outreach visits, reminders and financial incentives, that aim to improve adherence cost money to enact [65]. Thus, as first described by Fenwick et al. in 2008 [63], this adds another level (i.e. the implementation level) to the decision-making context: "In a budget-constrained healthcare system, the decision to invest in strategies to improve the implementation of cost-effective technologies must be made alongside decisions regarding investment in the technologies themselves and investment in further research." In order to simultaneously address the problem of allocating funds between these separate but linked activities, they propose a framework that reflects a simple four-state world where both information and implementation can be either at the current level or "perfect". This framework allows determining the maximum return to further research as well as an upper bound on the value of adopting implementation strategies [63]. Subsequently, Hoomans et al. [65] showed that "the framework provides a simple and useful analytic tool for decision makers to address resource allocation problems between healthcare provision, further research and implementation efforts". In 2010, Willan and Eckermann [10] showed that allowing for imperfect implementation has a profound effect on optimal sample size, and expected net gain from trials, and they present methods for taking imperfect implementation into account in optimal global trial design and multiple stage trial design. Soeteman et al. [126] have applied the VOI and implementation framework to estimate the value of further research and active implementation of psychotherapy for personality disorders in The Netherlands. One of the methodological findings from this study is that data required for estimating the levels of current and future implementation, as well as the eligible population, are scarce [126]. Furthermore, the framework is based on the assumption that the level of future implementation is independent of the level of current implementation, which in reality may not be the case. Future studies should incorporate this relationship and extend the framework to estimating EVSI and the expected value of specific implementation (EVSIM) [126].

5 Discussion

This study provides a systematic and critical review of the evolving methods and applications of VOI in academia and practice. Overall, the review shows a rapidly accumulating literature base on VOI roughly from 1999 onwards for methodological papers and from 2005 onwards for applied ones. The current literature base provides comprehensive coverage of methodological aspects of VOI including papers on the rationale and principles of VOI, its (potential) role in decision making, methods to develop and optimize VOI analyses, and additional or alternative approaches to VOI like the value of implementation or option values.

The literature base for applied papers to serve as a source for decision makers initially lagged behind by about 5 years, but caught up rapidly. It is important to note, however, that although many applied VOI studies proclaim to be 'real-life applications', it is unclear to what extent the recommendations of these studies can be and are actually used to inform decision making. Indeed, it often remains unclear which actual decision the undertaken VOI analysis is aiming to inform, e.g. whom it is explicitly informing (i.e. which commission, clinicians, institution, government or otherwise), if and which contextual factors are important to the decision at stake and how these may have influenced the structuring of the decision problem, and whether it is actually the 'decision time' from a decision maker's point of view rather than the academic research agenda. The predominance of methodological and illustrative applications, rather than true applications of VOI, is also reflected in the finding that most papers are published in methodological or general health economics journals; few (applied) papers are published in clinical journals.

Both the methodological and the applied VOI literature base are dominated by papers describing EVPI and characterize EVPI as an upper bound for EVSI with the notion that an EVPI >0 is a necessary but not sufficient condition to undertake further research. The sufficient condition for the worth of further research requires that the EVSI exceeds the costs of specific research [20, 37]. The results of this review indeed show that EVSI receives ample attention in the methodological papers. However, the results also reveal that EVSI still remains under-represented in the applied papers, indicating that the methods for estimating EVSI are yet to find common ground in the applied side of the healthcare decision-making arena. One of the hurdles to achieving this may well be the computational expense of undertaking an EVSI analysis, as noted in almost all papers on EVSI. Yet another potential reason for the underuse of EVSI (one that received far less attention in the literature) is that only about 50 % of the applications (data not presented in Table 1 in the Appendix) take a societal perspective in their analyses. This may greatly underestimate the overall value of the sample information collected [5] as, for example, CEAs that adopt a provider perspective do not account for the uncertainty surrounding parameters that are of potential benefit to other users of the drug or technology under study, or to other decision contexts in which the societal perspective is required.

As regards the EVPPI, the results show that this method has established itself fairly well in VOI applications, notably after 2006. In this year also a critical paper by Koerkamp et al. [42] was published, arguing that "the general recommended method to estimate EVPPI is conceptually and mathematically incorrect", as it estimates EVPPI as the reduction in expected opportunity loss instead of the increase in expected value. In the same paper, a method was proposed to overcome this problem [42].

As the starting point for any VOI analysis is the notion of uncertainty, appropriate characterization of uncertainty is of utmost importance in this field. The results of this review show that (second-order) parameter uncertainty is generally well accounted for by specifying a probability distribution for each of the main model parameters. Stochastic (first-order) uncertainty was not considered in any of the papers. Also, none of the applied papers used microsimulation (or first-order Monte Carlo simulation) to address the issue of interdependency between model parameters. Furthermore, while structural uncertainty typically has a stronger impact on VOI estimates than it has on cost-effectiveness outcomes, only two applied VOI papers appropriately accounted for structural uncertainty [70, 71]. One of the reasons for the latter might be that, up to approximately 2009, no guidance was available on how to appropriately account for structural uncertainty. In 2009, Bojke et al. [131] concluded in their review of methods to characterize uncertainty that "only parameterizing the uncertainty directly in the model can inform the decision to conduct further research to resolve this source of uncertainty". They also noted that the distinction between parameter and structural uncertainty may be "rather false and unhelpful" and that "one could argue that there is just uncertainty" and "making distinctions about its source is somewhat arbitrary". More recently, however, a step-by-step guide for handling methodological, structural and parameter uncertainty in decision-analytic models was published [133], which should help analysts and decision makers to characterize or assess uncertainty in a more appropriate and standardized way. Furthermore, a method to account for structural uncertainty using Bayesian model averaging was published in 2011 [54], which should lead to improved handling of uncertainty in VOI analyses in the future.

A better characterization of uncertainty may also help to reduce the possibility that additional information would reveal overconfidence in the current characterization of uncertainty, which would lead to an underestimation of the benefit of information collection in some cases. This phenomenon of increasing uncertainty after new information was collected—and thus a previously underestimated VOI—has been explained by Hammitt [134] and Hammitt and Shlyakther [135] and was recently observed by Vallejo-Torres et al. [73], in their application of VOI alongside the development cycle of a medical device. Hammitt and Shlyakther [135] also examined the role of surprise in estimating VOI and proposed a so-called 'value-of-surprise index' to correct for potential overconfidence and underestimation of the expected VOI when developing prior distributions and when combining distributions obtained from multiple experts. In 2011, Welton and Ades [55] aimed "to make sense of the concept of uncertainty in a … CEA model". They particularly focused on the relationship between data from a new study and the CEA model when there is heterogeneity. They concluded that "careful consideration of the relationship between existing (and future) evidence and the CEA model is required to provide practical VOI methods that can help research funders prioritize new research in the face of heterogeneity" [55]. Nevertheless, the notion of 'value of surprise' should remind decision analysts and decision makers that VOI in its current form examines uncertainty based on a theory of

probability (i.e. statistical uncertainty) and does not account for the value of unknown information (i.e. epistemic uncertainty) [58, 136].

The challenges of VOI for academia and practice are plentiful. Some of these challenges have been described in detail in the Results section, along with potential approaches to dealing with them. Yet there may be one overarching challenge that needs some further discussion here, which is that VOI, due to its (perceived) analytic complexity, is "not necessarily intuitive to decision and policy makers in healthcare" [100]. And yet, in our efforts to solve important challenges like high computational demands, and dealing with non-linear models and interdependency between parameters, estimations of effective time horizons and patient populations as well as structural uncertainties, we are rapidly increasing the complexity of VOI even further. However, in order to move the concept of VOI from what some call an academic pastime to a valid and practical tool for real-life decision support, a balance should be sought between the complexity and validity, and transparency and usability of VOI methods. While the Occam's razor approach to VOI of Eckermann et al. [1] is likely a step in the right direction, gathering a better insight into the needs and preferences of decision makers regarding VOI remains crucial in order for VOI to be appropriately used to assist in healthcare decision making. A recent study to provide such insights, although not explicitly on VOI, is the study of Longworth et al. [137] in which a list of priority topics for methods research to support decision making at NICE was established based on responses from members of the NICE secretariat and its advisory bodies, and representatives from academia, industry and other organizations working closely with NICE. Furthermore, an Agency for Healthcare Research and Quality (AHRQ) study reported that stakeholders found "modelling and VOI to be potentially useful tools, but there are a variety of methodological and operational issues that need to be considered and resolved if these methods are to be used to assist with prioritizing research gaps identified through systematic reviews" [35]. Apart from issues regarding technical expertise and model complexity, an important need, expressed in the AHRQ study, was to identify ways for comparing "the impact of different prioritization methods on the likelihood that priority questions will be answered through research" [35]. In addition, future user needs studies on VOI should evaluate how important VOI estimates are compared with other criteria that are commonly considered in healthcare and research funding decisions, e.g. equity considerations, and to what extent inclusion of VOI information actually would influence funding priorities, relative to the current process.

6 Conclusion

VOI analysis receives increasing attention in both the methodological and the applied literature bases. EVSI is generally accepted to be the preferred type of VOI to inform decision making regarding specific future studies, but real-life applications of EVSI have remained relatively scarce until now, (mainly) due to computational challenges. Other methodological challenges to VOI include dealing with non-linear models and interdependency between parameters, estimations of effective time horizons and patient populations, and structural uncertainties. For many of these challenges, analytic solutions have been proposed in the literature. Yet, as most of these are likely to further increase the analytic complexity of VOI and decrease VOI's transparency to decision makers, Occam's razor [1] should be seriously considered in application of these methods. Further VOI research should therefore include the development of leaner methods to arrive at valid VOI estimates. As important, however, is gaining better insight into the needs and preferences of decision makers in order for VOI to be appropriately incorporated into decision making on new therapies, optimally designing research studies and setting research priorities for health technology assessment.

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Author contributions Lotte Steuten conceived and planned the review, contributed to acquisition, analysis and interpretation of the data, drafted the paper, made substantive suggestions for revision, approved the final submitted version and acts as guarantor for the overall content. Gijs van de Wetering contributed to acquisition, analysis and interpretation of the data, drafted the paper, made substantive suggestions for revision, and approved the final submitted version. Karin Groothuis-Oudshoorn and Valesca Retèl contributed to acquisition, analysis and interpretation of the data, made substantive suggestions for revision and approved the final submitted version.

Appendix

See Appendix Table 1

Table 1 Overview of papers included in the systematic review

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Felli and Hazen [14] *Medical Decision Making*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI	Characterizing uncertainty	NA	NA
Claxton [15] *Health Economics*	Methodological Describe the (potential) role of VOI in regulatory processes	EVPI, EVSI, ENBS	None mentioned	NA	NA
Claxton and Thompson [16] *Journal of Health Economics*	Methodological Describe VOI rationale and key principles/ methods	EVSI, ENBS	None mentioned	NA	NA
Claxton et al. [24] *International Journal of Technology Assessment in Health Care*	Methodological Describe the (potential) role of VOI in regulatory processes	EVPI, EVPPI, EVSI, ENBS	Characterize parameter uncertainty in absence of good quality data	NA	NA
Meltzer [37] *Journal of Health Economics*	Methodological Developing or optimizing (mathematical) methods for VOI	VOI, EVPI (plus maximum VOI)	Developing meaningful priors concerning the parameters of decision models	NA	NA
Ades and Cliffe [38] *Medical Decision Making*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI	Dealing with parameters in correlated structures; estimating EVPI on functions of parameters	NA	NA
Karnon [58] *Health Policy*	Methodological Additional uses or adaptations to VOI	VOI, EVPI, EVPPI, EVSI, ENBS	Estimating effective population; characterizing uncertainty (structural uncertainty and unknown parameters)	NA	NA
Chilcott et al. [26] *Health Technology Assessment*	Methodological Describing the (potential) role of VOI in regulatory processes	EVPI, EVSI, ENBS	Estimating time horizon; evidence collection and synthesis; determining number of simulations for stable results	NA	NA
Ginnelly and Manca [69] *Applied Health Economics and Health Policy*	Applied Demonstration	EVPI, EVPPI	Computational cost; characterizing uncertainty	Adoption/ reimbursement; further research	Markov models; parameter uncertainty
Townsend et al. [25] *Health Technology Assessment*	Methodological Describe the (potential) role of VOI in regulatory processes	VOI, EVSI, ENBS	Computational cost; increasing transparency; account for the likely policy response to additional information, instead of assuming a totally rational model of behaviour	NA	NA

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Claxton et al. [75] *Health Technology Assessment*	Applied Real-life application	VOI, EVPI, EVPPI	Structuring decision problems; synthesizing evidence; computational cost	Adoption/ reimbursement; further research	Markov models; parameter uncertainty
Ades et al. [39] *Medical Decision Making*	Methodological Developing or optimizing (mathematical) methods for VOI	EVSI	Computational cost; prior parameter correlation	NA	NA
Fleurence and Torgerson [28] *Health Policy*	Methodological Describe the (potential) use of VOI in regulatory processes	EVPI	Addressing the practical issue of implementing the results of VOI analysis in clinical practice	NA	NA
Tappenden et al. [40] *Health Technology Assessment*	Methodological Developing or optimizing (mathematical) methods for VOI	VOI, EVPI, EVPPI, EVSI, ENBS	Estimating the effective population; development of criteria for selecting a metamodelling approach; using metamodelling for EVSI and ENBS analysis	NA	NA
Yokota and Thompson [27] *Risk Analysis*	Methodological Describe the (potential) role of VOI in regulatory processes	VOI, EVPI, EVPPI, EVSI	Complexity of solving VOI problems with continuous probability distributions as inputs in models; characterizing uncertainty	NA	NA
Yokota and Thompson [6] *Medical Decision Making*	Methodological Describe the (potential) role of VOI in regulatory processes	VOI, EVPI, EVPPI, EVSI, ENBS	Computational complexity; prior parameter correlation	NA	NA
Claxton et al. [17] *Health Affairs*	Methodological Describe VOI rationale and key principles/ methods	VOI	Structuring decision problems; synthesizing evidence; characterizing uncertainty	NA	NA
Ginnelly et al. [76] *Applied Health Economics and Health Policy*	Applied Real-life application	EVPI, EVPPI	Structuring decision problems; characterizing uncertainty	General health policy; further research	Markov model; parameter uncertainty
Martikainen et al. [77] *PharmacoEconomics*	Applied Real-life application	EVPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty
Miller [59] *PharmacoEconomics*	Methodological Describe the (potential) role of VOI in regulatory processes	VOI, EVPI, EVPPI, EVSI, ENBS	Account for relationship between economic information and customer behaviour	NA	NA

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Robinson et al. [78] *Health Technology Assessment*	Applied Real-life application	EVPI	Accounting for sunk costs and complete reversibility in decision making; combining a normative evidence-based decision model with clinicians' own personal behavioural perspective	Adoption/ reimbursement; further research	Markov model and decision tree; parameter uncertainty
Sculpher and Claxton [18] *Value in Health*	Methodological Describe VOI rationale and key principles/ methods	EVPI, EVPPI	Structuring decision problems; synthesizing evidence; characterizing uncertainty	NA	NA
Willan and Pinto [41] *Statistics in Medicine*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI, EVSI, ENBS	Estimating the effective lifetime of the technology	NA	NA
Ades and Sutton [19] *Journal of the Royal Statistical Society, Series A*	Methodological Describe VOI rationale and key principles/ methods	EVPI, EVSI	Evidence synthesis; elicitation of priors	NA	NA
Brown et al. [79] *Health Economics*	Applied Real-life application	EVPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty
Castelnuovo et al. [80] *Health Technology Assessment*	Applied Real-life application	EVPI, EVPPI	Computational cost	Adoption/ reimbursement; further research	Markov models; parameter uncertainty
Claxton and Sculpher [81] *PharmacoEconomics*	Applied Real-life application	VOI, EVPI, EVPPI	Structuring decision problems; characterizing uncertainty (including structural); evidence synthesis; computational cost	Adoption/ reimbursement; further research	Markov models; parameter uncertainty
Fenwick et al. [20] *Medical Decision Making*	Methodological Describe VOI rationale and key principles/ methods	EVPI, EVPPI	Complexity and computational challenges of non-conjugate prior distributions	NA	NA
Garside et al. [82] *Health Technology Assessment*	Applied Real-life application	EVPI	None mentioned	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Koerkamp et al. [42] *Health Economics*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPPI	Computational cost; non-linearity between parameters and net benefit	NA	NA
Henriksson et al. [83] *Health Economics*	Applied Real-life application	EVPI, EVPPI	None mentioned	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Iglesias and Claxton [84] *PharmacoEconomics*	Applied Real-life application	EVPI	None mentioned	Adoption/ reimbursement; further research	Markov model; parameter uncertainty

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Philips et al. [21] *International Journal of Technology Assessment in Health Care*	Methodological Describe VOI rationale and key principles/ methods	EVPI, EVPPI	Estimating impact of heterogeneity between patient subgroups; account for gap between information and implementation of VOI	NA	NA
Sculpher and Drummond [29] *PharmacoEconomics*	Methodological Describe the (potential) role of VOI in regulatory processes	VOI	Evidence synthesis; estimating impact of heterogeneity between locations; unjustified variation in methods guidelines	NA	NA
Speight et al. [85] *Health Technology Assessment*	Applied Real-life application	EVPI, EVPPI	Characterizing uncertainty; heterogeneity between patient subgroups	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Fleurence [70] *Health Economics*	Applied Demonstration	EVPI	Analytic feasibility; addressing the practical issue of implementing the results of VOI analysis in clinical practice	General health policy; further research	Markov model and decision tree; parameter uncertainty; structural uncertainty
Bojke et al. [86] *PharmacoEconomics*	Applied Real-life application	EVPI	None mentioned	Adoption/ reimbursement; further research	Markov model; parameter uncertainty, structural uncertainty
Brennan et al. [43] *Medical Decision Making*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPPI	Estimating effective population and effective lifetime of technology; characterizing uncertainty	NA	NA
Brennan and Kharroubi [44] *Journal of Health Economics*	Methodological Developing or optimizing (mathematical) methods for VOI	EVSI	Dealing with unequal sample sizes between study arms; establishing the best value from a range of research study options, rather than the optimal *n* for a particular study; characterizing uncertainty of unknown parameters; perspective of the decision maker might not be societal; accounting for global value of further research	NA	NA
Brennan and Kharroubi [45] *Health Economics*	Methodological Developing or optimizing (mathematical) methods for VOI	EVSI	Computational cost	NA	NA
Colbourn et al. [87] *Health Technology Assessment*	Applied Real-life application	EVPI, EVPPI	None mentioned	Adoption/ reimbursement; further research	Decision tree; parameter uncertainty
Collins et al. [88] *Health Technology Assessment*	Applied Real-life application	EVPI (plus implementation)	Prior parameter correlation	Adoption/ reimbursement; further research	Markov model; parameter uncertainty

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Dong et al. [89] *International Journal of Technology Assessment in Health Care*	Applied Real-life application	EVPI, EVPPI	Time horizon over which the evidence is relevant differs for different items of information	General health policy; further research	Markov model; parameter uncertainty
Eckermann and Willan [7] *Health Economics*	Methodological Additional uses or adaptations to VOI	EVSI	None mentioned	NA	NA
Girling et al. [90] *International Journal of Technology Assessment in Health Care*	Applied Real-life application	EVPI, EVPPI, EVSI	Characterizing uncertainty (in unknown parameters)	R&D decision making	Regression-based model; parameter uncertainty
Griebsch et al. [91] *International Journal of Technology Assessment in Health Care*	Applied Real-life application	EVPI	None mentioned	Adoption/ reimbursement; further research	Decision tree; parameter uncertainty
Groot Koerkamp et al. [60] *Medical Decision Making*	Methodological Additional uses or adaptations to VOI	EVPI	Representing correlations between the outcomes of alternatives	NA	NA
Quinn et al. [92] *American Journal of Kidney Diseases*	Applied Real-life application	EVPI, EVPPI	None mentioned	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Teerawattananon et al. [93] *Value in Health*	Applied Real-life application	EVPI, EVPPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty
Willan [30] *Clinical Trials*	Methodological Describe the (potential) role of VOI in regulatory processes	EVSI	Characterizing parameter uncertainty; estimating the effective population	NA	NA
Barton et al. [46] *Value in Health*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI	None mentioned	NA	NA
Bojke et al. [71] *Medical Decision Making*	Applied Demonstration	EVPI	Computational cost; estimating the effective population and lifetime of technology; prior parameter correlation	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Claxton [31] *PharmacoEconomics*	Methodological Describe the (potential) role of VOI in regulatory processes	VOI, EVPI, EVPPI	Computational cost	NA	NA

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Coyle and Oakley [47] *European Journal of Health Economics*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPPI	Computational complexity	NA	NA
Eckermann et al. [61] *Medical Decision Making*	Methodological Additional uses or adaptations to VOI	EVPI	None mentioned	NA	NA
Eckermann and Willan [62] *Medical Decision Making*	Methodological Additional uses or adaptations to VOI	EVSI	None mentioned	NA	NA
Eckermann and Willan [11] *Value in Health*	Methodological Developing or optimizing (mathematical) methods for VOI	EVSI	Accounting for time in EVSI calculations	NA	NA
Fenwick et al. [63] *Medical Decision Making*	Methodological Additional uses or adaptations to VOI	EVPI	Account for relationship between information and implementation; characterize uncertainty about the current level of implementation; valuation of specific implementation strategies	NA	NA
Fenwick et al. [48] *Value in Health*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI	Dealing with censored data in VOI	NA	NA
Galani et al. [94] *Value in Health*	Applied Real-life application	EVPI, EVPPI	Computational cost	General health policy; further research	Markov model; parameter uncertainty
Grant et al. [95] *Health Technology Assessment*	Applied Real-life application	EVPI, EVPPI	None mentioned	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Griffin et al. [22] *Journal of Health Services Research and Policy*	Methodological Describe VOI rationale and key principles/ methods	EVPI, EVPPI	Structural and parameter uncertainty; ability to reflect quality of data and potential bias of data sources	NA	NA
Koerkamp et al. [96] *Radiology*	Applied Real-life application	EVPI, EVPPI, EVSI, ENBS	None mentioned	General health policy; further research	Model type not described; parameter uncertainty
Oostenbrink et al. [97] *Value in Health*	Applied Real-life application	EVPI, EVPPI	Estimating costs of follow-up study	General health policy; further research	Markov model; parameter uncertainty
Philips et al. [49] *Medical Decision Making*	Methodological Developing or optimizing (mathematical) methods for VOI	VOI, EVPI	Estimation the effective population and the effective lifetime of the technology	NA	NA

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Ramsey et al. [100] *Medical Care*	Applied Real-life application	EVSI, ENBS	Analytic complexity; not necessarily intuitive to policy makers	General health policy; further research	Decision tree; parameter uncertainty
Rojnik and Naversnik [32] *Value in Health*	Methodological Describe the (potential) role of VOI in regulatory processes	EVPI, EVPPI	Computational cost; non-linearity	NA	NA
Singh et al. [98] *International Journal of Technology Assessment in Health Care*	Applied Real-life application	EVPI	None mentioned	General health policy; further research	Decision tree; parameter uncertainty
Somerville et al. [99] *European Journal of Cancer*	Applied Real-life application	EVPI, EVPPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty
Wailoo et al. [101] *Value in Health*	Applied Real-life application	EVPI, EVPPI	Estimating effective lifetime of new technologies; taking into account that reducing uncertainty has a value for other decisions in addition to the treatment of, in this case, influenza; characterizing uncertainty (including structural uncertainty)	General health policy; further research	Decision tree; parameter uncertainty
Welton et al. [50] *Journal of the Royal Statistical Society, Series A*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI, EVPPI, EVSI	Dealing with multiple sources of uncertainty; computational cost	NA	NA
Willan [64] *Clinical Trials*	Methodological Additional uses or adaptations to VOI	EVSI, expected net gain	Account for sensitivity of trial results to market share, per-patient profit and incidence; assuming that sample sizes involved ensure that the relevant test statistics are Normally distributed	NA	NA
Willan and Kowgier [56] *Health Economics*	Methodological Developing or optimizing (mathematical) methods for VOI	EVSI	Accounting for time for accrual, follow-up and analysis in EVSI	NA	NA
Baio and Russo [34] *PharmacoEconomics*	Methodological Describe the (potential) role of VOI in regulatory processes	EVPI	None mentioned	NA	NA
Bansback et al. [102] *PharmacoEconomics*	Applied Real-life application	EVPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Black et al. [103] *Health Technology Assessment*	Applied Real-life application	EVPI	None mentioned	Adoption/ reimbursement; further research	Decision tree; parameter uncertainty
Carlson et al. [104] *Value in Health*	Applied Real-life application	EVPI	None mentioned	R&D decision making	Markov model; parameter uncertainty
Conti and Claxton [57] *Medical Decision Making*	Methodological Developing or optimizing (mathematical) methods for VOI	ENBS	Computational costs; non-linearity between parameters and net benefit	NA	NA
Eckermann and Willan [9] *Health Economics*	Methodological Developing or optimizing (mathematical) methods for VOI	ENBS	Extending the ENBS framework to allow for optimal trial design and decision making across jurisdictions	NA	NA
Ehlers et al. [105] *British Medical Journal*	Applied Real-life application	EVPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty
Goeree et al. [33] *Journal of the American College of Radiology*	Methodological Describe the (potential) role of VOI in regulatory processes	EVPI, EVPPI	Generalizability of efficacy evidence to real-world effectiveness; transferability of clinical effectiveness, economic data, or patient preference information across jurisdictions	NA	NA
Hassan et al. [106] *Radiology*	Applied Real-life application	EVPI, EVPPI	Structural uncertainty	General health policy; further research	Markov model; parameter uncertainty
Hassan et al. [107] *Radiology*	Applied Real-life application	EVPI, EVPPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty
Hoomans et al. [65] *Value in Health*	Methodological Additional uses or adaptations to VOI	EVPI	Allowing for the cost of reversal; allow for dynamic relation between level of information and level of implementation	NA	NA
Janssen and Koffijberg [66] *Value in Health*	Methodological Additional uses or adaptations to VOI	VOI, EVPI	Providing insight in the expected shift in costs and effects as compared with the currently preferred intervention	NA	NA
McKenna et al. [108] *Health Technology Assessment*	Applied Real-life application	EVPI, EVPPI, EVSI, ENBS	Generalizability	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Miners [109] *Haemophilia*	Applied Real-life application	EVPI, EVPPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty
Rogowski et al. [110] *Health Technology Assessment*	Applied Real-life application	EVPI, EVPPI	EVPI does not provide both a necessary and a sufficient condition, even if the cost of trialling falls below this amount, because a trial will resolve only a proportion of the uncertainty	Adoption/ reimbursement; further research	Markov model; parameter uncertainty

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Stevenson et al. [111] *Medical Decision Making*	Applied Real-life application	EVSI, ENBS	None mentioned	General health policy; further research	Decision tree; parameter uncertainty
Wilson et al. [112] *British Journal of Surgery*	Applied Real-life application	EVPI, EVPPI	Accounting for structural uncertainty	General health policy; further research	Decision tree; parameter uncertainty
Xie et al. [113] *Clinical Therapeutics*	Applied Real-life application	EVPI, EVPPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty
Griffin et al. [67] *Medical Decision Making*	Methodological Additional uses or adaptations to VOI	EVPI, EVPPI	Calculating the VOI from alternative sequential research designs that account for learning from the information gathered on each parameter in sequence	NA	NA
Groot Koerkamp et al. [51] *Medical Decision Making*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI, EVPPI, EVSI, ENBS	Dealing with patient heterogeneity in decision models and VOI analysis	NA	NA
Groot Koerkamp et al. [72] *Value in Health*	Applied Demonstration	EVPI, EVPPI, EVSI and partial EVSI	Technical complexity of VOI	Further research	Model type not stated; parameter uncertainty
Grutters et al. [114] *Cancer Treatment Reviews*	Applied Real-life application	EVPI, EVPPI	None mentioned	Adoption/ reimbursement; further research	Model type not stated; parameter uncertainty
Smits et al. [115] *Radiology*	Applied Real-life application	EVPI	None mentioned	General health policy; further research	Markov model and decision tree; parameter uncertainty
Hassan et al. [116] *Diseases of the Colon and Rectum*	Applied Real-life application	EVPI, EVPPI	None mentioned	Further research	Decision tree; parameter uncertainty
Hoyle [52] *Value in Health*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI	Estimating the expected lifetime of technology for VOI analysis	NA	NA
Kim et al. [117] *BMC Complementary and Alternative Medicine*	Applied Real-life application	EVPI	None mentioned	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
McKenna et al. [118] *Health Technology Assessment*	Applied Real-life application	EVPI, EVPPI	Sensitivity of EVPI estimates to evidence synthesis approach used	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Stevenson et al. [119] *Health Technology Assessment*	Applied Real-life application	EVPI, EVPPI	None mentioned	Adoption/ reimbursement; further research	Model type not stated; parameter uncertainty
Stevenson et al. [120] *Value in Health*	Applied Real-life application	EVPI, EVPPI	None mentioned	General health policy; further research	Model type not stated; parameter uncertainty

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Willan and Eckermann [10] *Health Economics*	Methodological Additional uses or adaptations to VOI	EVSI, ENBS	Allow for expected effect of imperfect implementation on EVSI and ENBS	NA	NA
Barton [53] *Health Economics*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI	To explore what happens to EVPI as the number of options in the decision problem increases	NA	NA
Brush et al. [121] *Health Technology Assessment*	Applied Real-life application	EVPI	EVPI analysis can provide only an indication of potential worth for further information, as any research undertaken will reduce rather than eliminate uncertainty	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Hall et al. [122] *PharmacoEconomics*	Applied Real-life application	EVPI	None mentioned	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Lal et al. [68] *Journal of Translational Medicine*	Methodological Additional uses or adaptations to VOI	VOI	Use of VOI in a wider policy and healthcare systems valorization framework for genome-based technology	NA	NA
Latimer et al. [123] *PharmacoEconomics*	Applied Real-life application	EVPI, EVPPI	Dealing with structural uncertainty; simultaneously consider observational and experimental data in the VOI analysis	Further research	Markov model incorporating within-state decision trees; parameter uncertainty
Myers et al. [35] AHRQ *Future Research Needs: Methods Research*	Methodological Describe the (potential) role of VOI in regulatory processes	VOI	Compare the impact of different prioritization methods; identifying appropriate (technical) resources for analysis; defining appropriate timing of modelling; identify appropriate level of modelling complexity	NA	NA
Nosyk et al. [124] *PLoS One*	Applied Real-life application	EVPI	None mentioned	General health policy; further research	Markov model; parameter uncertainty
Price et al. [54] *Value in Health*	Methodological Developing or optimizing (mathematical) methods for VOI	EVPI	Dealing with structural uncertainty	NA	NA
Purmonen et al. [125] *Acta Oncologica*	Applied Real-life application	EVPI, EVPPI	None mentioned	Adoption/ reimbursement; further research	Combined decision tree and Markov model; parameter uncertainty
Soeteman et al. [126] *Value in Health*	Applied Real-life application	EVPI, EVPPI and EVPIM	Estimating eligible population and level of implementation; assumption that level of implementation is independent from level of information	Adoption/ reimbursement; further research	Markov model; parameter uncertainty

Table 1 continued

Study and journal	Type (methodological or applied) and main aim of the paper	Type of VOI (general VOI; EVPI, EVPPI, EVSI, ENBS)	Main challenge(s)	Applied papers	
				Decision to be informed	Modelling characteristics (type of model; type of uncertainty considered)
Vallejo-Torres et al. [73] *Medical Decision Making*	Applied Demonstration	EVPI, EVPPI	Integrating VOI in technology development cycle	Further research; R&D decision making	Decision tree; parameter uncertainty
Welton and Ades [55] *Health Economics*	Methodological Developing or optimizing (mathematical) methods for VOI	VOI	Interpretation of heterogeneity in CEA models and relationship with VOI	NA	NA
Welton et al. [23] *Rheumatology*	Methodological Describe VOI rationale and key principles/ methods	EVPI, EVPPI, EVSI, ENBS	Role of VOI analysis in deciding whether head-to-head trials are needed	NA	NA
Woods et al. [74] *Value in Health*	Applied Demonstration	EVPI, EVPPI	None mentioned	Adoption/ reimbursement; further research	Markov model; parameter uncertainty
Gurusamy et al. [127] *Applied Health Economics and Health Policy*	Applied Real-life application	EVPI, EVPPI	None mentioned	Adoption/ reimbursement; further research	Decision tree; parameter uncertainty
Maheswaran and Barton [128] *PLoS One*	Applied Real-life application	EVPI, EVPPI	None mentioned	Further research	Markov model; parameter uncertainty

AHRQ Agency for Healthcare Research and Quality, *CEA* cost-effectiveness analysis, *ENBS* expected net benefit of sampling, *EVPI* expected value of perfect information, *EVPIM* expected value of perfect implementation, *EVPPI* expected value of partial perfect information, *EVSI* expected value of sample information, *NA* not applicable, *VOI* value of information

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