Methods Future Research Needs Report

Number # 6

Minimal Modeling Approaches to Value of Information Analysis for Health Research

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The information in this report is intended to help health care researcher and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Minimal Modeling Approaches to Value of Information Analysis for Health Research

Structured Abstract

Value of information (VOI) techniques can provide estimates of the expected benefits from clinical research studies. These VOI estimates can inform decisions about the design and priority of those studies. Most VOI studies use decision analytic models to characterize the uncertainty of the effects of interventions on health outcomes. For some potential applications of VOI, the complexity of constructing such models poses barriers to practical application of VOI. However, because some clinical studies can directly characterize uncertainty in health outcomes, it may sometimes be possible to perform VOI analysis with only minimal modeling. This paper (1) develops a framework to define and classify minimal modeling approaches to VOI; (2) reviews existing VOI studies that apply minimal modeling approaches; and (3) illustrates and discusses the application of the minimal modeling to two new clinical applications to which the approach appears well suited because clinical trials with comprehensive outcomes provide preliminary estimates of the uncertainty in outcomes. We conclude that minimal modeling approaches to VOI can be readily applied to in some instances to develop estimates of the expected benefits of clinical research.

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Introduction

Biomedical research, including clinical research, is believed to have very large returns.[1] However, funds for this research are limited relative to the vast number of research questions that could be studied. This makes decisions about how to allocate clinical research spending especially important. For example, systematic reviews of clinical topics, such as those performed by the United States (U.S.) Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (http://www.ahrq.gov/clinic/epc/), often identify many research gaps, and decisions need to be made about how to prioritize those research gaps, within and across clinical topics. Techniques to prospectively estimate of the value of research could potentially improve the outcomes of research spending. However, predicting the value of research is difficult because the outcomes of research are inherently uncertain and the value of those uncertain outcomes may be difficult to characterize.

Value of information (VOI) analysis provides a coherent theoretical framework for estimating the expected benefits from clinical research studies. These estimates can aid in the design and prioritization of those studies. Performing VOI analysis requires mechanisms to characterize the uncertainty of the effects of interventions being studied on outcomes. This involves both determining which of the options being considered is preferred for all the possible outcomes of the study, and determining what the value of that preferred option is as compared to the alternatives. Most VOI studies use decision analytic models to characterize this uncertainty. However, the complexity of constructing such models makes VOI difficult to apply and limits its implementation.

Clinical studies that directly characterize uncertainty in comprehensive measures of health outcomes (e.g., both quality-adjusted life-years [QALYs] and costs) make it possible to perform VOI analysis with only minimal modeling, which we define as VOI that is performed without full disease and/or decision analytic modeling. To accomplish this, uncertainty in patient-level outcomes for VOI can be bootstrapped from the results of clinical trials that report a comprehensive outcome measure, which we define as a measure sufficient to conclude whether one outcome for a patient is better or worse than another outcome. A clinical trial that directly measures the effect of an intervention on quality-adjusted life expectancy is the most obvious example of this, but studies of interventions that have their main effects in terms of quality of life are still potentially amenable to minimal modeling by constructing only a simple model of survival (perhaps based on standard life tables). In practice, the minimal modeling approach is most likely to be applicable to interventions for which effects on survival or quality of life occur quickly enough to be measured directly in a clinical trial.

The purpose of this paper is to define and demonstrate a "minimal modeling approach" to VOI that can be used to prioritize research. We begin by outlining a theoretical framework for estimating the expected population value of information from conducting research, which we then use to define and categorize existing approaches to VOI as either "full modeling" or "minimal modeling." We further distinguish two subtypes of minimal modeling approaches to VOI: "limited modeling," and "no modeling," which we define and discuss in detail in the Theoretical Framework chapter. We review existing VOI studies in the Literature Review chapter, focusing on those that describe and apply minimal modeling approaches. In the Applications chapter, we illustrate and discuss the application of minimal modeling VOI methods to two new clinical applications: (1) the use of azithromycin versus amoxicillin/clavulanate in the treatment of acute bacterial sinusitis; and (2) the use of erlotinib

plus gemcitabine versus gemcitabine alone in the treatment of pancreatic cancer. These applications were selected because published results from clinical trials were available that provided preliminary estimates of the uncertainty in comprehensive outcomes as defined above.

Our results confirm that minimal approaches to VOI can be readily applied to estimate the expected benefits of research in instances where data on comprehensive measures of outcomes are available. These results suggest that minimal modeling can offer an advantage over traditional VOI analysis when rapid or low-cost estimates of the value of research are needed. They also suggest that minimal modeling approaches can be a useful complement to adaptive clinical trial design because the data collected at each stage of an adaptive trial can serve as a basis for minimal modeling to inform subsequent stages of the trial.[2]

Theoretical Framework

Value of information analysis for health research seeks to estimate the expected value of research projects at the population level. To do so, it begins with a person-level estimate of the value of research to reduce uncertainty surrounding the net benefit of alternatives treatments or interventions under consideration. Specifically, let θ describe a parameter vector that determines the net benefit of treatment option j to be studied, which we denote as $NB(\theta, j)$. Net benefit is most commonly defined as net monetary benefit, which can be calculated by taking the benefit in monetary terms of some improvement in health and subtracting any costs. The monetary value of improvements is most commonly calculated by multiplying the gain in health by some measure of the monetary value per unit of health gained (e.g., QALYs gained multiplied by $ per QALY).* Furthermore, let $\max_j E_\theta NB(\theta, j)$ describe the expected value of the decision from among j interventions that maximizes expected net benefit given current information. The value of research is defined by identifying the information set $\{I\}$ consisting of a set of outcomes and associated probabilities that could result from a particular research activity. Equation 1 describes the expected value of information (EVI) from research on a per-person basis.

Eq. 1. $$EVI = E_I \max_j E_{\theta|I} NB(\theta, j) - \max_j E_\theta NB(\theta, j)$$

Several additional factors need to be considered to translate the value of research at the person level to a population statistic potentially relevant for informing policy. First, because research has value for populations of people and over time (t), it is important to account for the incidence ($Incidence_t$) of the relevant condition (i.e., annual rate of new cases per member of the population) and the size of the relevant at-risk population ($Population_t$). Another factor that should be considered is the likelihood that relevant information may be imperfectly implemented, and thus produce value for only a fraction of the population in whom it could have been applied ($\text{Im}plementation_t$). In addition, VOI may account for the possibility that that future cohorts would not benefit from the research because the value of the information is not durable over time because improved treatments are introduced, and/or new clinical evidence emerges that may greatly increase or decrease the expected clinical benefit of a treatment independent of the research study being considered ($Durability_t$). Finally, benefits accruing to more distant future cohorts may be valued less than benefits for less distant cohorts, causing benefits to future cohorts to be discounted at a rate β_t where $\beta_t < 1$. Thus, the population-level expected value of information ($pEVI$) is:

Eq. 2. $$pEVI = \sum_t \beta^t \times Durability_t \times Implementation_t \times Incidence_t \times Population_t \times EVI$$

Equation 2 lays out the basic framework for the VOI framework when it is fully applied. In practice, application of this framework is almost never complete. In some cases, it is because

*Alternatively, net health benefit can be calculated by taking health gains in QALYs and subtracting the health that could be obtained by applying the costs of the intervention in a health intervention that was at the threshold for cost-effectiveness (e.g., $50,000 per QALY).[3]

cutting-edge theoretical issues such as value of information were simply not considered by the individuals performing the VOI analysis. In other cases, a factor is considered, but without much rigorous analysis. For example, durability is sometimes modeled by considering benefits that only accrue over a time horizon of 5 to 10 years, generally with little or no justification or consideration of the fact that the results of research may take some time to be implemented, or that irreversible decisions made today (such as surgery) may have highly durable effects. In other cases, critical issues such as the size of the affected population are modeled without much thought for the practical effects of research across populations.

For example, VOI analyses performed by the National Institute for Health and Clinical Excellence (NICE) typically are based on the size of the United Kingdom population (~60 million), which is 20 percent of the size of the U.S. population (300 million), 12 percent of the size of the European Union, and less than 1 percent of the world population (7 billion). Since research done in one country is generally also of value outside that country, it is clear that estimates of the value of research that take a single-country perspective can severely underestimate the value of research on a global scale, and that comparisons of the value of research from different countries based on the size of the local population can be severely misleading as to the net value of research.[4] Of course, since the cost of research is usually borne by one country, there is some justification for the traditional practice of focusing on just that country's population if that country discounts benefits to other countries.

Most commonly, however, VOI calculations are not fully implemented because of the lack of critical pieces of information. For example, it may be very difficult to fully characterize the possible outcomes of a research study, and their likelihood. Similarly, it may be difficult to meaningfully characterize the uncertainty in the net benefit of the alternatives under consideration, particularly when there is little or no prior clinical data on relevant outcomes. In these circumstances, decision models are often used in these to obtain estimates of comprehensive measures of (net) benefit, based on data on aspects of the decision in question. Decision models have the advantage of permitting calculation of the expected value of partial perfect information (*EVPPI*), which describes the value of information on specific parameters in a complex decision model, and identifies the most important parameters to target for study. The use of decision models to perform VOI also has drawbacks. One big drawback is the issue of transparency in modeling and in assumptions (a common challenge for decision analysis in general). Perhaps the most important drawback is that VOI studies based on decision analyses can be very time consuming and complex so that the approach is too burdensome for practical application in some circumstances.

The practical challenges in applying VOI have led to both led to both theoretical and practical efforts to simplify the application of value of information approaches. Some factors, such as implementation and durability, are simply ignored on a routine basis. This causes VOI calculations in general to overestimate the true benefits of research. When it is difficult to characterize the extent to which a particular research study is likely to reduce uncertainty, the expected value of perfect information (*EVPI*) is often used to provide an upper bound on the value of research by calculating the expected value of research that would eliminate all uncertainty in the net benefit of treatment. This is possible because EVPI depends only on the distribution of the net benefit of the treatment options being considered (Equation 3).

Eq. 3. $$EVPI = E_\theta \max_j NB(\theta, j) - \max_j E_\theta NB(\theta, j)$$

When even this uncertainty cannot be fully characterized—for example, because little or nothing is known about the effectiveness of the treatments being considered—EVPI can also be bounded by measures of the total burden of disease that could potentially be eliminated.5 The advantages of these bounding approaches are that they are easier to apply so that they can be used to triage potential topics if an upper bound suggests that the potential value of research is not large. They can also be applied when a great deal of potentially relevant information on uncertainty or the potential information that could come from research is lacking. However, a major limitation is that it is not generally possible to know how close such upper bounds would be to more complete analyses. Thus upper bounds will again be informative mostly when they suggest that the potential value of research is not large.

When good data are not available to characterize the uncertainty associated with a treatment, decision models are often used to characterize uncertainty in net benefit. These models typically describe a series of health states, a mathematical model to describe transitions among health states (e.g., a decision tree to describe the likelihood of events within periods and a Markov model to describe transitions over time), and a set of payoffs (e.g., utility and costs) associated with each health state. Because the construction of these models can be very complex and time consuming, approaches that are easier to apply would be helpful. This is especially true when a decision tree is to be used for VOI analysis, since that also necessitates characterizing the uncertainty associated with each parameter. Cost-effectiveness analyses done alongside clinical trials[6] in which comprehensive outcomes measures (at least in terms of direct measures of QALYs and costs) are collected directly, avoid the need for the construction of models and also allow uncertainty in these outcomes to be directly quantified.

Minimal Modeling Approaches

We define minimal modeling approaches to VOI as those that model VOI without constructing a decision model of the disease and treatment process to characterize the uncertainty in net benefit associated with an intervention.

As previously discussed, minimal modeling approaches to VOI are feasible in certain circumstances. One situation in which minimal modeling VOI is feasible is when a prior clinical trial provides data on a comprehensive measure of the net benefit of the interventions examined. In general, this would require a trial that directly measures all health benefits in QALYs and all costs. To be valid representations of the net benefit of the treatments that are compared while avoiding modeling, such trials would need to measure these comprehensive outcomes until the point that there are no differences between the treatments examined. Examples would include studies that followed all patients to death or that followed all patients until they recovered. These approaches require no modeling to calculate the individual level of value of information, and we, therefore, term them “no modeling” approaches. VOI calculations based on no modeling can be done mathematically or via bootstrapping/simulation. Bootstrapping/simulation, replicating or resampling decision values, can be done using raw patient-level data on relevant parameters (i.e., a nonparametric approach) or by making parametric distributional assumptions.

Another situation in which it may not be necessary to build a full decision model of the disease and treatment process is when the treatment does not affect survival but only quality of life and quality of life is directly measured by a clinical trial. In such cases, which we term “limited modeling,” it is necessary to build a survival model, but the model does not require developing a full model of health states that predicts survival (e.g., progression of cancer

between stages, psychosis to completed suicide). The recent analysis of the value of research on atypical antipsychotics is an example of such a study.[7]

Table 1 briefly outlines and summarizes these three the modeling approaches to VOI calculations (full, limited, and no modeling), their potential scope applicability, and the advantages and disadvantages of these alternative approaches.

Table 1. Modeling approaches to VOI calculations

Approaches	Definitions*	VOI Calculations	Data Requirements	Clinical Application(s)	Advantages (+) and Disadvantages (-)
Full Modeling	Full characterization of the disease/ treatment using a decision model or other simulation model of relevant health state	Simulation/ bootstrapping, parametric and/or nonparametric	Data on all model parameters	Chronic conditions, complex diseases	- Complex and time-consuming modeling exercises
		Equation-based computation, parametric			+ Detailed uncertainty analysis and VOI estimates, including calculation of EVPPI
No Modeling	Direct replication or direct calculation of (incremental) effects on comprehensive health outcomes (e.g. QALYs, and/or net benefits)	Simulation/ bootstrapping, parametric and/or nonparametric	Distributions of comprehensive health outcomes or, QALYs and/or net benefits	Acute conditions, end of life treatments, direct measurement of final health outcomes	+ No need for complex and time-consuming modeling
		Equation-based computation, parametric			+ Complementary to adaptive clinical trial design
					- Requires clinical trial that can provide comprehensive measure of net benefit
					- No comprehensive uncertainty analysis and VOI estimates (EVPPI)
Limited Modeling	Any modeling necessary (e.g., modeling of patient survival, mapping of treatment effect to utilities or aggregate approximation of costs) without using a decision model or other simulation model of relevant health states	Simulation/ bootstrapping, parametric and/or nonparametric	Intermediate measures for health outcomes or QALYs, costs and/or NBs; Survival data	Acute conditions, end of life treatments	+ Reduced need for complex and time-consuming modeling
		Equation-based computation, parametric			+ Complementary to adaptive clinical trial design
					- Requires clinical trial that can requires only modeling of survival or other limited modeling to generate comprehensive measure of net benefit
					- No comprehensive uncertainty analysis and VOI estimates (EVPPI)

* All approaches seek to address specific treatment or coverage decisions, to characterize decision uncertainty and to establish VOI estimates

EVPPI =expected value of partial perfect information

Literature Review

We conducted a comprehensive review of both published, peer-reviewed literature and grey literature to identify and describe clinical research studies describing or applying minimal modeling approaches to VOI.

Search Strategy and Inclusion Criteria

We searched the MEDLINE database for English-language publications from January 1, 1990 to June 3, 2010, using the following exact search terms (in all fields): "value of information," "value of additional information," "value of information analysis," "expected value of perfect information," "EVPI," "expected value of partial perfect information," "EVPPI," "Bayesian approach to uncertainty," or "value of research." All titles and abstracts of the search results were screened by two investigators (DM and JC) to identify potentially relevant studies.

Our grey literature search was limited to Internet sites of different health technology assessment (HTA) organizations and institutions in the United States, Canada, the U.K., Australia/New Zealand, The Netherlands, and Germany. Web sites were searched for: (1) VOI methods guidance intended to aid authors in completing a HTA, and (2) examples of VOI applications in individual HTA and systematic review publications.

Studies were only included if they involved clinically related application or development of VOI analysis for estimating the value of research or prioritization of research. Studies focusing on the value of diagnostic testing to collect information to guide the treatment for individual patients did not meet our scope definition, and were not included in our review. In addition, the reference lists of relevant studies were checked.

Study Classification and Data Extraction

Based on the full-text reading, the investigators (DM, TH, JC, and AB) independently classified the publications as to whether (1) these involved "VOI theory/methods only," "VOI theory/methods with application," or "VOI application only," and (2) whether the approach to the VOI calculations comprised the use of a full model, limited modeling, or no modeling (Table 1).

We summarized theory and methods for those studies that appeared to adopt a minimal modeling approach. For each VOI application in the studies that were classified "VOI theory/methods with application" or "VOI application only" based on a "limited modeling" or "no modeling" approach, we extracted data on: the limited modeling component; the approach to VOI calculations (Table 1); the application and its setting; the perspective of analysis; the incidence (or prevalence) of the disease or condition; the time horizon of the decision problem (relating to durability); the approach (if any) to implementation issues; the discounting of costs and effects; and the cost-effectiveness results and VOI results (per patient and per population).

All data extraction was done by one investigator (TH), while the other investigators (DM, JC, and AB) performed a check for accuracy and completeness of the extracted data. Any disagreements about the classification of publications and the data extraction were resolved by consensus. We undertook a descriptive synthesis of the review results and compared VOI calculations across studies.

Results

Identification of Studies

Figure 1 is a flowchart that summarizes the process and results of our literature review. The MEDLINE database search produced 230 hits, while 120 studies were identified as potentially relevant following the screening of the abstracts and titles. On the basis of full-text reading of the 116 papers that we were able to collect, we identified 18 studies as "VOI theory/methods only," and 80 studies with some empirical application, including 24 studies with "VOI theory/methods with application(s)" and 56 "VOI application only." In total, we found 4 studies describing minimal modeling approaches only,[5, 8-10] while 8 VOI applications adopting a limited modeling approach were reported in 6 studies[7,11, 12[a,b,c],13-15] versus 9 VOI applications with no modeling in 12 studies.[4,16, 17[a,b], 18, 19[a,b], 20 [a,b]; 21-25]

In our grey literature search, 12 HTA organizations were identified, with only 2 organizations (i.e., NICE in the U.K. and the Dutch Health Care Insurance Board [CVZ] in The Netherlands) providing a small amount of guidance for the use of VOI methods. A search of all HTA publications from these organizations for VOI analysis produced 22 hits, 9 of which were previously identified in the MEDLINE search. Of the 13 new publications, we classified 12 as full VOI models, and one as minimal modeling with one application.[26] Table 2 summarizes these searches by country.

Theory/Methods on Minimal Modeling

Four papers described theory/methods related to limited modeling[5,8] or no modeling[9,10] without seeking to apply the theory/methods. Detsky (1985)[8] described how the cost-effectiveness of a clinical trial could be calculated with effectiveness measured in terms of deaths prevented; because a more comprehensive outcome measure (such as QALYs) was not used, no complex decision model was needed, so the paper provides an example of how a minimal modeling approach might be applied. Meltzer (2001)[5] focused on the development of bounding approaches such as the way in which burden of disease-type calculations and the expected value of perfect information could bound estimates of the value of information. Willan (2008)[9] argued that the potential for imperfect implementation of health technologies should be accounted for, such as by calculating VOI with current implementation. Janssen and Koffijberg (2009)[10] focused on the construction of VOI estimates with independent estimates of variability in benefits and costs.

Figure 1. VOI literature review flowchart

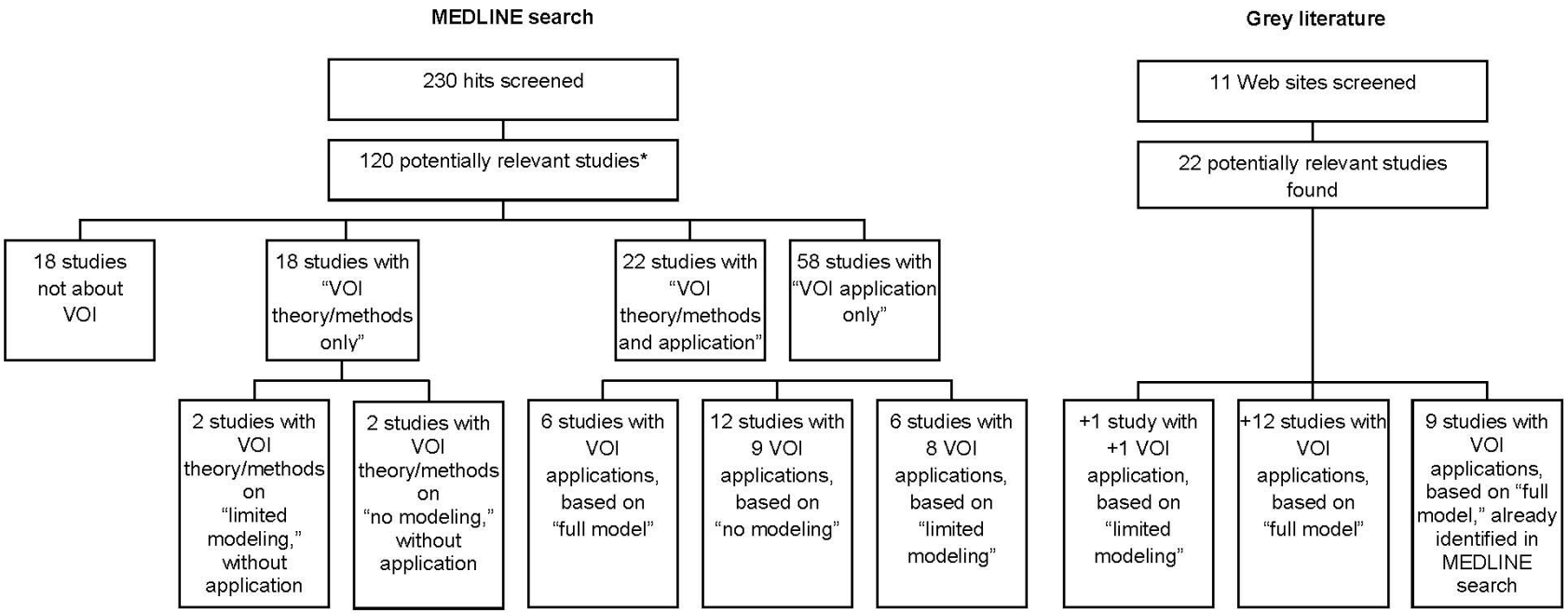


Table 2. Results of grey literature search, by country

Country	Search & Results
United States	We searched publications of the VA Technology Assessment Program and the Agency for Healthcare Research and Quality Effective Health Care Program, but identified no relevant VOI studies
United Kingdom	We searched NICE reports. The use of VOI analysis is advocated in published methods guidance.[27] Four technology appraisals used full modeling approaches for VOI calculations. One uses minimal modeling approaches and is included. Three full modeling VOI studies but no minimal modeling studies were identified in publications of the U.K. National Institute for Health Research Health Technology Assessment Program.
Canada	Five full-model VOI studies and no minimal-model studies were found among the publications of the Canadian Agency for Drugs and Technologies in Health Health Technology Assessment Program. Searches at the PATH Research Institute and Ontario Health Technology Assessment Series revealed no VOI studies.
Australia	Reports of the Medical Services Advisory Committee at the Australian Department of Health and Ageing, the Australian Safety and Efficacy Register of New Interventional Procedures - Surgical based in the Royal Australasian College of Surgeons produced no VOI studies.
New Zealand	Reports of Health Services Assessment Collaboration at the University of Canterbury funded by the New Zealand Ministry of Health produced no VOI studies.
The Netherlands	Reports of The Netherlands Organisation for Health Research and Development, which executes many reports funded by the Ministry of Health and The Netherlands Organisation for Scientific Research, included no VOI studies. Reports of the Dutch Health Care Insurance Board (CVZ) included guidance on uncertainty analysis in economic evaluation[28,29] that could include VOI but no full or minimal modeling VOI studies.
Germany	Reports of the German Institute for Quality and Efficiency in Health Care, which works under contract from the Federal Joint Committee and the Federal Ministry of Health, revealed no VOI studies.

VOI Applications using Minimal Modeling

Tables 3 and 4 provide details of the applications in the published studies that applied limited modeling and no modeling approaches to VOI calculations, respectively. In total, our review of the academic literature found 18 applications of VOI analysis in which either a limited modeling (50%) or no modeling (50%) approach was adopted. In the limited modeling studies, the modeling component commonly involved the approximation of patient survival or life expectancy, for example, using (declining) exponential distributions.

The majority of the minimal modeling studies involved pharmaceuticals or other clinical interventions, including surgical procedures[12,13,25] and medical devices.[14] Six VOI studies were conducted in the U.K., five in the United States, three in Canada, and two in The Netherlands, while four occurred across different jurisdictions (e.g., North America or the European Union). Five out of 18 VOI applications were undertaken from a societal perspective, as one would expect given the public characteristics of evidence collection.

As shown in Table 3, 7 of the 18 VOI applications were based on equation-based computations relying on parametric assumptions for the costs and effects of the health technologies under evaluation. This included two early studies by Detsky (1990)[11] and Omenn (2001)[16], and five recent and related studies by Willan and colleagues.[9,17,19-21] Four studies, three by Townsend and colleagues[12[a,b,c]] and the Detsky (1990)[11] study, adopted an alternative approach to minimal modeling in that the incremental cost-effectiveness ratios of future trials or evidence to be developed were calculated on the basis of prior information or elicitation of expert opinion of the cost and effects of the health technologies and costs of research. All the remaining eight VOI applications, reflecting the vast majority of the more recent studies, used simulation/bootstrapping of raw data on costs and effects (QALYs). Parametric

simulation/bootstrapping techniques (in R, Microsoft Excel, or Stata) were often used to explore decision uncertainty and establish VOI measures in these studies.

Most VOI application studies reported outcomes in terms of person level estimates of the value of information (e.g., *EVPI*). Population-level estimates of the value of information (e.g., *pEVPI*) were reported less commonly, despite that these measures establish the necessary and sufficient condition for decisionmaking about research funding. EVPI results varied from €2.1 ($2.89) to £1064 ($1675) per patient, while the population values for *pEVPI* ranged between €365,000 ($504,649) and $308 billion.[*] Where separate measures of benefits and costs were available, the value of partial information on benefits and costs was calculated in some cases.

[*] Foreign currencies converted to $US using October 2010 exchange rates.

Table 3. Details of applications (i=9) in VOI studies [k=7] using "limited modeling" approaches to VOI

Reference	Detsky, 1990[11]	Forbes et al, 2002[26]	Townsend et al., 2003[12] [ex. a]	Townsend et al., 2003[12] [ex. b]	Townsend et al., 2003[12] [ex. c]	Ramsey et al., 2008[13]	Meltzer et al., 2009[7]	Girling et al., 2007[14]	Stevenson et al., 2010[15]
Modeling of health outcomes [i.e. limited modeling component]	Life-years saved modeled using modified DEALE method	Life-years gained modeled using exponential distributions	-	-	-	Life-years gained (long term) modeled using DEALE method	Life-years gained modeled using pooled estimates from meta-analysis Incidence: distribution of survival curves and steady-state lifetime prevalence	Life-years gained modeled, using exponential (constant hazard) distribution, with mean survival from REMATCH [in OMM] and separate distributions for LVAD failures/successes	QALYs modeled by mapping from EPDS scores to utility values (SF-6D) and multiplying these values by appropriate time period, based on PoNDER trial data
Approach to value of information calculations	- Equation-based computations, parametric - Sensitivity analysis, varying trial sizes	Simulation/ bootstrapping, parametric	Scenario analysis, varying assumptions around trial evidence and implementation of CMSW service	Scenario analysis, varying assumptions around trials evidence and implementation of stabilization protocol	Scenario analysis, varying trial evidence and implementation of early elective surgery	Simulation/ bootstrapping, parametric	Simulation/boot-strapping, parametric	- Equation-based computations, parametric - Sensitivity analysis, varying assumptions around device costs	Simulation/ bootstrapping, parametric and nonparametric
Application	Comparison of five trials in cardiovascular medicine (LRC trial, RCT-portion of CASS, and MRFIT trial)	Liposomal doxorubicin vs. topotecan as second-line treatment in patients with advanced ovarian cancer	Postnatal midwifery support service and standard current midwifery visits vs. midwifery visits alone	Prehospital intravenous fluid replacement vs. stabilization alone in adults with serious trauma	Early surgery vs. a period of ultrasound surveillance for patients aged 60–76 years with small AAAs	Lung–volume-reduction surgery (LVRS) vs. medical therapy (MT) for patients with severe emphysema	Perphenazine (first-generation antipsychotics) vs. all second-generation antipsychotics for patients with schizophrenia	Left ventricular assist devices (LVADs) implantation optimal medical management (OMM) in patients with end-stage heart failure (ESHF)	Group cognitive behavior therapy (gCBT) vs. routine primary care for women with postnatal depression
Setting	U.S.	U.K.	U.K.	U.K.	U.K.	U.S.	U.S.	U.K.	U.K.
Perspective	NOT STATED	NHS	NOT STATED	NHS	NHS	NIH / CMS	NIH	Health care provider	NHS

Table 3. Details of applications (i=9) in VOI studies [k=7] using "limited modeling" approaches to VOI (continued)

Reference	Detsky, 1990[11]	Forbes et al, 2002[26]	Townsend et al., 2003[12 [a]]	Townsend et al., 2003[12 [b]]	Townsend et al., 2003[12 [c]]	Ramsey et al., 2008[13]	Meltzer et al., 2009[7]	Girling et al., 2007[14]	Stevenson et al., 2010[15]
Data	Costs and effects of trials, health services delivery: 5 trials	- Patient survival: no difference [ITT] [PPO in sensitivity analysis], trial 30-49] - Costs: trials 30-49[30]	- Δ-point GHP scale of SF-36: varying assumptions - CMSW service costs: approximations - Implementation of service: expert opinion	- Patient mortality: varying assumptions - Prehospital care services costs: approximations - Development of prehospital care services and implementation of stabilization protocol: expert opinion	- Patient mortality, QoL (MOS): varying assumptions - Costs of aortic grafting/ regular observation: approximations - Development of treatment of small AAAs and implementation of early elective surgery: expert opinion	- Patient survival (short term): NETT trial - Costs of LVRS procedures: single center study[31] - Medical costs for patient with COPD: National Medical Expenditure Survey - Utility weights: HUI-III data from pilot study - Trial cost: assumptions	- QoL/costs: CATIE study [Normal/Gamma distribution] - Prevalence, mortality: secondary analysis - Trial costs: assumptions	- LVAD failures/ successes, mean survival, utilities; treatment costs: REMATCH trial - Device costs: assumptions - Prior distributions for survival: elicitation from experts [uniform distributions]	- EPDS scores: RCT[32] - Cost of providing gCBT, duration of comparative advantage for gCBT: RCT[32 and] expert opinion
Incidence [prevalence]	15k – 5M	3000	UK birth rate	Number of trauma patients treated by a non-metropolitan ambulance service	2000	20k	52.6k [CATIE trial]	15k	120k
Time horizon	NOT STATED	5 years	5 years	10 years	5/10 years	10 years	Lifetime / 30 years / 20 years	10 years	10 years
Discounting	NOT STATED	Effects and costs: 6%	Effects: 2%, costs: 6%	NOT STATED	NOT STATED	Effects and costs: 3%	Effects and costs: 3%	Effects and costs: 3.5%	NOT STATED

Table 3. Details of applications (i=9) in VOI studies [k=7] using "limited modeling" approaches to VOI (continued)

Reference	Detsky, 1990[11]	Forbes et al, 2002[26]	Townsend et al., 2003[12] [a]	Townsend et al., 2003[12] [b]	Townsend et al., 2003[12] [c]	Ramsey et al., 2008[13]	Meltzer et al., 2009[7]	Girling et al., 2007[14]	Stevenson et al., 2010[15]
Cost-effectiveness results	-	ICER = £22k/life-year[§] [Pr(CE) = 0.80]*	ICER = £2-3.50/ per +1-point GHP scale of SF-36	ICER = £3000-4330/life saved	ICER = £20k/life-year saved	ICER = $305k/QALY [Pr(CE) = 0.04]	$796k/QALY [Pr(CE) = 0.45]	NB = -£46.8k [Pr(CE) = 0.002]*	ICER = £36k/QALY [Pr(CE) = 0.2]
Value of information results [per patient]	ICERs of trials = $5461-102k/life-year	EVPI ≈ £800*	-	-	-	-	-	EVPI = £6*	EVPI = £53.50*
Value of information results [per population]	-	pEVPI ≈ £10.7M* [§] deterministic, * λ = £30k/life-year	-	-	-	pEVPI = $46.0M* pEVSI = $41.0M* pENBS = -$19.0M, SS = 1250/arm* * λ = $50k/QALY	pEVPI = $308B pENBS = $13.8B, SS ≈ 4000-4500/arm * λ = $50k/QALY	pEVPI = £775k* *λ = £30k/QALY, device costs = £60k[32]	pEVPI = £64M* * λ = £30k/QALY

AAAs = abdominal aortic aneurysms; λ = cost-effectiveness threshold; CASS = Coronary Artery Surgery Study; CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; CI = confidence interval; DEALE = Declining Exponential Average Life Expectancy; GHP = General Health Perception; ICER = incremental cost-effectiveness ratio; LRC = Lipid Research Clinics-Coronary Primary Prevention Trial; MRFIT = Multiple Risk Factor Intervention Trial; NB = net benefit; NETT = National Emphysema Treatment Trial;; pENBS = population expected net benefit of sampling; pENG = population expected net gain [equivalent to pENBS]; pEVPI = population expected value of information; pEVSI = (population) expected value of sample information; Pr(CE) = probability that health care technology is cost-effective; QALY = quality-adjusted life-year; SS = sample size

Table 4. Details of applications [k=9] in VOI studies [n=12] using "no modeling" approaches to VOI

Reference	Omenn, 2001[16]	A: Willan and Pinto, 2005[17][a] B: Eckermann and Willan, 2007[18] C: Willan and Kowgier, 2008[19][a] D: Eckermann and Willan, 2009[4] E: Willan and Eckermann, 2010[20][a]	A: Willan and Pinto, 2005[17][b] C: Willan and Kowgier, 2008[19][b]	Willan, 2007[21]	Barton et al., 2008[22]	Fenwick et al., 2008[23]	Groot Koerkamp et al., 2008[24]	Groot Koerkamp et al., 2010[25]	Willan and Eckermann, 2010[20][b]
Modeling of health outcomes	Specificity and sensitivity of testing based on assumptions [see also Data]	Direct measurement of QALYs [see also Data]	Direct measurement of QALYs [see also Data]	Direct measurement of risk of cardiovascular event [see also Data]	Direct measurement of QALYs [see also Data]	Direct measurement of life-years gained [see also Data]	Conversion of EuroQol-scores into utility values using Dolan tariff	Conversion of EQ5D-scores to utilities using Dutch scoring algorithm	Direct measurement of dyspepsia symptoms [see also Data]
Approach to VOI calculations	Equation-based computations, parametric	Equation-based computations, parametric	Equation-based computations, parametric	Equation-based computations, parametric	Simulation/ boot-strapping, parametric	Simulation/boots trapping, nonparametric	Simulation/boots trapping, parametric	Simulation/boots trapping, parametric and nonparametric	Equation-based computations, parametric
Application	National Toxicology Program carcinogenicity test vs. MultiCASE prediction of potential carcinogenic risk	Early (week 34) vs. late (week 37) external cephalic version (ECV) in pregnant women presenting in the breech position	Prednisone plus mitoxantrone vs. prednisone alone in patients with hormone-resistant prostate cancer	Ramipril (ACE inhibitor) vs. management strategies of placebo in patient over 55 years at risk	Comparison of seven different management strategies for GERD	Rate- vs. rhythm-control treatments for persons with atrial fibrillation	Radiography and magnetic resonance (MR) imaging vs. radiography alone in patients with acute knee trauma (in an ED setting)	Endovascular revascularization vs. supervised exercise training for patients with intermittent claudication	Omeprazole plus metronidazole/ clarithromycin vs. omeprazole plus placebos in patients with dyspepsia
Setting	U.S.	A,B,C,E: North America; D: US, UK and Australia	All: Canada	U.S. and Canada	Canada	U.S.	The Netherlands (NL) / European Union (EU)	The Netherlands	Canada
Perspective	NOT STATED	All: Societal	All: Societal	Government/private donation-based or philanthropic agency	Provincial government payer	Third-party payer	Societal	Societal	Societal

Table 4. Details of applications [k=9] in VOI studies [n=12] using "no modeling" approaches to VOI (continued)

Reference	Omenn, 2001[16]	A: Willan and Pinto, 2005[17][a] B: Eckermann and Willan, 2007[18] C: Willan and Kowgier, 2008[19][a] D: Eckermann and Willan, 2009[4] E: Willan and Eckermann, 2010[20][a]	A: Willan and Pinto, 2005[17][b] C: Willan and Kowgier, 2008[19][b]	Willan, 2007[21]	Barton et al., 2008[22]	Fenwick et al., 2008[23]	Groot Koerkamp et al., 2008[24]	Groot Koerkamp et al., 2010[25]	Willan and Eckermann, 2010[20][b]
Data	- Specificity, sensitivity, costs of testing: assumptions - Social cost of false positive and false negative testing: assumptions	All: QALYs: pilot study[34] no differences bet. jurisdictions [assumptions] All: Costs: no difference, no differences bet. jurisdictions [assumptions] All: Trial costs: assumptions B,E: Accrual rate; time period for data collection/analysis: assumptions C: Probability of stopping: assumptions B: Reversal cost: assumptions E: Implementation: assumptions	All: QALYs, costs: Canadian trial[35, 36] All: Trial costs: assumptions C: Probability of stopping: assumptions	- Risk of cardiovascular event, costs: HOPE study - Trial costs: assumptions	QALYs, costs: replication of previous analyses[37]	Survival and cost: AFFIRM trial, patient level data	- EuroQoL-scores, (non)medical costs: RCT[38] - Trial costs: assumptions	- EQ5D-scores, (non)medical costs: RCT[39] - Trial cost: assumptions	- Dyspepsia symptoms, costs: Cadet Hp-trial[40] - Trial costs: assumptions - Accrual rate, time period for data collection/analysis: assumptions

Table 4. Details of applications [k=9] in VOI studies [n=12] using "no modeling" approaches to VOI (continued)

Reference	Omenn, 2001[16]	A: Willan and Pinto, 2005[17][a] B: Eckermann and Willan, 2007[18] C: Willan and Kowgier, 2008[19][a] D: Eckermann and Willan, 2009[4] E: Willan and Eckermann, 2010[20][a]	A: Willan and Pinto, 2005[17][b] C: Willan and Kowgier, 2008[19][b]	Willan, 2007[21]	Barton et al., 2008[22]	Fenwick et al., 2008[23]	Groot Koerkamp et al., 2008[24]	Groot Koerkamp et al., 2010[25]	Willan and Eckermann, 2010[20][b]
Incidence [prevalence]	US population	A: NOT STATED B,E: 50k C: 100k D: 50k (U.S.), 10k (U.K.), 3k (Australia)	A: 10k C: 60k	NA	NA	500k [2.3M]	20k (NL) / 561k (EU)	10k	50k
Time horizon	NOT STATED	All: 20 years	All: NOT STATED	4.5 years [HOPE study]	1 year	5.65 years	10 years	5 years	20 years
Discounting	NA	A: NOT DONE B,C,D,E: NOT STATED	A: NOT DONE C: NOT STATED	Costs: 3%	NA	Effects and costs: 3%	Effects and costs: 3%	Effects and costs: 3%	NOT STATED
Cost-effectiveness results	-	-	-	-	ICERs = $7755, $12,183, $110.8k/QALY [Pr(CE) ≈ 0.33, 0.18, 0.45]	ICER = $4.98M/life-year gained [Pr(CE) = 0.51]	NB = €2467 [95% CI = €515, €4419]*	NB = €2170 [95% CI = €-2818, €6685]	-
Value of information results [per patient]	-	-	-	Threshold number of patients benefiting from technology = 4.8M (U.S.); 2.28M (Canada)*	EVPI ≈ $14*		EVPI = €2.1*		-

Table 4. Details of applications [k=9] in VOI studies [n=12] using "no modeling" approaches to VOI (continued)

Reference	Omenn, 2001[16]	A: Willan and Pinto, 2005[17][a] B: Eckermann and Willan, 2007[18] C: Willan and Kowgier, 2008[19][a] D: Eckermann and Willan, 2009[4] E: Willan and Eckermann, 2010[20][a]	A: Willan and Pinto, 2005[17][b] C: Willan and Kowgier, 2008[19][b]	Willan, 2007[21]	Barton et al., 2008[22]	Fenwick et al., 2008[23]	Groot Koerkamp et al., 2008[24]	Groot Koerkamp et al., 2010[25]	Willan and Eckermann, 2010[20][b]
Value of information results [per population]	pEVPI = $62,0M	A: pENG = $0.7M, SS = 346/arm* B: pENG = $0.4M, SS = 284/arm*,§ C: pENG = $1,4M, SS = 155/arm (stage 1), 124/arm (stage 2)* D: Global pENG = 0, global SS = 0/arm (U.S.), 0, 0/arm (U.K.), $0.9M, 339/arm (Australia) E: pENG = 38.2M, SS = 489/arm*,†	A: pENG = $0, SS = 0/arm C: pENG = $1.6M, SS = 66/arm (stage 1), 163/arm (stage 2)*	-	-	pEVPI: $23M*	- pEVPI: €365k (NL) / €10.2M (EU)* - pENBS = NA (NL) / €3,8M, SS = 2500/arm (EU)*	- pEVPI = €11.0M* - pENBS = €7.3M, SS = 475/arm*	pENG = $8.0M, SS = 109/arm *

Table 4. Details of applications [k=9] in VOI studies [n=12] using "no modeling" approaches to VOI (continued)

Reference	Omenn, 2001[16]	A: Willan and Pinto, 2005[17][a] B: Eckermann and Willan, 2007[18] C: Willan and Kowgier, 2008[19][a] D: Eckermann and Willan, 2009[4] E: Willan and Eckermann, 2010[20][a]	A: Willan and Pinto, 2005[17][b] C: Willan and Kowgier, 2008[19][b]	Willan, 2007[21]	Barton et al., 2008[22]	Fenwick et al., 2008[23]	Groot Koerkamp et al., 2008[24]	Groot Koerkamp et al., 2010[25]	Willan and Eckermann, 2010[20][b]
		* λ = $1000/non-caesaran delivery (U.S. and U.K.); $750 (Australia) § Reversal cost = $ 2.0 M † γ = 0.67, β = 2.33	* λ ≈ $20k/QALY	* λ = $10k/cardiovascular event saved	* λ = $50k per QALY	* λ = $50k/life-year	* λ = €80k/QALY	* λ = €80k/QALY	*λ = $1,000/year without/minimal dyspepsia symptoms, γ: 0.67, β = 2.33

λ = cost-effectiveness threshold; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; CI = confidence interval; ICER = incremental cost-effectiveness ratio; NA: not applicable; NB = net benefit; pENBS = population expected net benefit of sampling; pENG: population expected net gain, equivalent to (p)ENBS; pEVPI = population expected value of information; pEVSI = population expected value of sample information; Pr(CE) = probability that health care technology is cost-effective; QALY = quality-adjusted life-year; SS = sample size

Comparison of VOI Calculations Using Minimal Modeling

Perhaps not surprisingly, given that the minimal modeling approach to VOI is driven primarily by empirical concerns, most of the papers we found that discussed approaches we would classify as discussing minimal modeling approaches to VOI were empirical applications. Aside from the fact that the results of VOI studies vary with the uncertainty in the costs and effects of the health technologies under evaluation, the results of such analyses are often difficult to compare due to variation in the perspective and time horizon for the analysis, the size of population targeted and the actual use or implementation of health technologies in the specific settings. Moreover, difference may exist in the approach to decision analysis (e.g., nonparametric bootstrapping vs. parametric equation-based computations), the use of end outcomes (e.g., clinical events avoided vs. QALYs), and the threshold value for cost-effectiveness in the jurisdictions in which the VOI analysis is applied.

Some of these differences in study assumptions (such as discount rates and assumptions about the value of a QALY) almost certainly cannot even approximately be adjusted for based on the published results, which makes it nearly impossible to compare value of research calculations across studies. However, some differences across studies, such as the population studies (e.g., U.K. vs. U.S.), time horizon (e.g., 5 or 10 years), currency (e.g., $, £, €), and year can be fairly readily adjusted for. To demonstrate this, we attempted to compare results across minimal modeling studies (i.e., limited modeling and no modeling studies) for all studies possible. Populations from the different studies were normalized to reflect the U.S. population, with a horizon of 10 years and denominated in 2010 U.S. dollars using historical currency exchange rates and the general U.S. Consumer Price Index.

As shown in Tables 5 and 6, standardizing on these factors often had large effects on the value of research, suggesting the importance of developing approaches to standardize population level VOI analyses if they are to be compared to each other. Estimates of the standardized VOI varied from around $2 million to nearly $125 billion, with most studies distributed broadly across the range from $2 million to $600 million. The $125 billion study, analyzing uncertainty in the value of atypical antipsychotics in schizophrenia, reflects to large degree the fact that schizophrenia affects 1 percent of the population throughout their entire life, and the substantial uncertainty about the effects of these medications on both quality of life and costs.

Table 5. Comparison of VOI estimates across limited modeling studies

Reference	Detsky, 1990	Forbes et al, 2002	Townsend et al., 2003 [a]	Townsend et al., 2003 [b]	Townsend et al., 2003 [b]	Ramsey et al., 2008	Meltzer et al., 2009	Girling et al., 2007	Stevenson et al., 2010
Year of study	-	2000	-	-	-	1996	2002	2007	2008
Country	-	U.K.	-	-	-	U.S.	U.S.	U.K.	U.K.
Per Patient VOI	-	£800.00	-	-	-	-	-	£6.00	£53.50
Population VOI in Millions	ICER-Trial	£11	ICER-Trial	ICER-Trial	ICER-Trial	$46	$308,000	£1	$64
Applied scale factor for population at risk*	-	5.01	-	-	-	1.00	1.00	5.01	5.01
Applied scale factor for time horizon	-	2.00	-	-	-	1.00	0.33	1.00	1.00
Applied (historical) currency exchange rate†	-	1.52	-	-	-	1.00	1.00	2.00	1.86
Consumer price index factor‡	-	1.27	-	-	-	1.39	1.21	1.05	1.01
Calculated standardized pEVPI (in $1,000,000)	NA	$206	NA	NA	NA	$64	$124,658	$8	$603

SS = sample size; ICER-T = incremental cost-effectiveness ratio of trial; pEVPI = population expected value of information; pENG = population expected net gain to conducting trial; EVSI = expected value of sampling

* 2010 estimates by the Population Division of the United Nations Department of Economic and Social Affairs, http://en.wikipedia.org/wiki/List_of_countries_by_population

† OANDA, http://www.oanda.com/currency/historical-rates, average daily over period 01/01/year of study and 12/31/year of study

‡ US Department of Labor, Bureau of Labor Statistics, CPI Inflation Calculator, http://www.bls.gov/data/inflation_calculator.htm

Table 6. Comparison of VOI stimates across no modeling studies

Reference	Omenn, 2001	[A: Willan and Pinto, 2005 [1]]; [B: Eckermann and Willan, 2007]; [C: Willan and Kowgier, 2008 [CT] [1]]; [D: Eckermann and Willan, 2009]; [E: Willan and Eckermann, 2010]	[E: Willan and Pinto, 2005 [2]]; [F: Willan and Kowgier, 2008 [CT] [2]]	Willan 2007 [CT]	Barton et al., 2008	Fenwick et al., 2008	Groot Koerkamp et al., 2008	Groot Koerkamp et al., 2010	Willan and Eckermann, 2010
Year of study	2001	-	-	-	2000	2002	2000	2005	-
Country	U.S.	-	-	-	U.S.	U.S.	The Netherlands	The Netherlands	-
Per Patient VOI	-	-	-	EVSI/ENG	$14	-	€ 2.10	-	-
Population VOI in Millions	$62	pENG, SS	pENG, SS	-	-	$23	€ 0.37	€ 11	pENG, SS
Applied scale factor for population at risk*	1.0	-	-	-	13975§	1	19	19	-
Applied scale factor for time horizon	1	-	-	-	10	1.77	1	2	-
Applied (historical) currency exchange rate†	1.00	-	-	-	1.00	1.00	0.92	1.25	-
Consumer price index factor‡	1.23	-	-	-	1.27	1.21	1.27	1.12	-
Calculated standardized pEVPI (in $1,000,000)	$76	NA	NA	NA	$2	$49	$8	$573	NA

SS = sample size; ICER-T = incremental cost-effectiveness ratio of trial; pEVPI = population expected value of information; pENG = population expected net gain to conducting trial; EVSI = expected value of sampling

* 2010 estimates by the Population Division of the United Nations Department of Economic and Social Affairs, http://en.wikipedia.org/wiki/List_of_countries_by_population

† OANDA, http://www.oanda.com/currency/historical-rates, average daily over period 01/01/year of study and 12/31/year of study

‡ U.S. Department of Labor, Bureau of Labor Statistics, CPI Inflation Calculator, http://www.bls.gov/data/inflation_calculator.htm

§ http://books.google.com/books?id=WSP6wdD_8MEC&pg=PA21&lpg=PA21&dq=incidence+GERD+usa&source=bl&ots=wK3IeR74Vv&sig=URVMDq1Dt-xW63bB5qiM4nNKN9k&hl=en&ei=QzTGTJP4LM3Angenh_2nAQ&sa=X&oi=book_result&ct=result&resnum=1&ved=0CBUQ6AEwADgU#v=onepage&q=incidence%20GERD%20usa&f=false

Applications

To assess the potential of minimal modeling approaches to provide information on the prospective value of research, we discuss two new clinical applications that do not require survival modeling. In the first application, we study azithromycin versus amoxicillin/clavulanate in acute bacterial sinusitis. We chose this application as an example where the outcome is something other than mortality, and because the treatments differ only in the rate at which symptoms resolve and in their costs. In the second application, we study erlotinib and gemcitabine versus gemcitabine alone in pancreatic cancer. This application was chosen because we were able to find published clinical trials that follow patients to an endpoint of death. Appendix A provides details of both applications.

Application 1: No survival modeling with no survival effects—the case of azithromycin versus amoxicillin and clavulanate in acute bacterial sinusitis

Background and Setting

In the United States, approximately 1 billion cases of acute rhinosinusitis and 20 million cases of acute bacterial rhinosinusitis are diagnosed every year. About 50 percent of people with clinically diagnosed acute sinusitis have a bacterial sinus infection. Antibiotics are the primary treatment for such infections, and they help in early resolution of symptoms. A recent comparative effectiveness study compared a single 2-gram dose of azithromycin extended release to 10 days of amoxicillin/clavulanate (875 mg/125 mg) twice daily. The primary outcome was resolution of symptoms within 5 days.[41] At day 5, 70/236 patients (29.7%) in the azithromycin extended-release arm and 45/238 patients (18.9%) in the amoxicillin/clavulanate arm had resolution of symptoms (difference: 10.8%; 95% confidence interval [CI]: 3.1–18.4%). By day 28, 26/236 patients (11.0%) in the azithromycin extended release arm and 27/238 patients (11.3%) in the amoxicillin/clavulanate arm had used additional antibiotics (difference: -0.4%; 95% CI: -6.1% to 5.3%). Additional physician visits, quality of life, and overall satisfaction were similar between groups. Since the single dose of azithromycin is more expensive than the course of amoxicillin/clavulanate, the superior outcomes with azithromycin raise questions also of cost-effectiveness.

Aims

We sought to determine what the expected value of additional studies would be to verify the superiority of azithromycin in terms of (1) days to symptom resolution, and (2) the net benefit of azithromycin, where the extra costs of treatment are subtracted from the benefits (denominated in monetary units).

Modeling of Health Outcomes, Approach to VOI Calculations, and Data

We used a no-modeling approach to VOI. First, we used published data on time to symptom resolution presented in the form of survival curves to recover the individual level data for time to

symptom resolution under the two treatment arms. As a validation of this exercise, we were able to closely replicate the published data on the survival curves, the hazard ratio, and its significance using our individual level data. These are presented in Appendix B. Mean time to symptom resolution within 14 days of treatment initiation for each treatment was obtained by averaging the time to symptom relief over patients in each arm. One thousand bootstrap replicates of the individual-level data provided the distribution of the mean time to symptom relief under each arm. This distribution is shown in Appendix B.

To calculate net benefit, we accounted for both uncertainty in time to symptom resolution and willingness to pay (WTP) and subtracted costs of treatment from their product. Using average wholesale prices reported in the Red Book, 10 days of oral amoxicillin/clavulanate potassium 875 mg/125 mg every 12 hours was found to be $31.99 (2010 prices) while a single oral dose of azithromycin extended release (2 g) was found to be $55.68.[42] The mean WTP was $73.2 (Standard Error [SE]=6.66) in 2010 U.S. dollars.

We estimated the individual level value of perfect information by bootstrap sampling out of the distribution of average benefits and costs and averaging the net benefit of azithromycin over amoxicillin/clavulanate whenever azithromycin had a positive net benefit.

Perspective, Incidence, Time Horizon, and Discounting

Our population EVPI calculations were based on an annual incidence of 10 million cases of infected acute sinusitis. We arbitrarily chose a 10-year horizon for our analysis assuming that a superior treatment would become available by that time. A 10-year horizon also sits approximately between the expiration dates Pfizer has for extended-release azithromycin in the tablet (U.S. Patent 6,068,859, exp. 5/30/2017) and suspension forms (U.S. Patent 6,984,403, exp. 2/14/2024). We used a discount rate of 3 percent.

Cost-Effectiveness Results and Decisions Based on Current Information

Patients receiving azithromycin extended release had a mean time to resolution of 7.55 days (SE=0.260) compared to 8.12 days (SE=0.210) for patients receiving amoxicillin/clavulanate (p value for difference 0.077). Based on currently available information on time to symptom resolution only, the treatment decision should be the use of azithromycin extended release. The net benefit of treatments is calculated based on valuing faster time to resolution using a published estimate of mean WTP for preventing a day of sinus congestion collected through a population-based survey.[43] Based on expected net benefit criteria, current treatment decision would still be azithromycin extended release (= [8.12 − 7.55] * $73.20 − [$55.68 − $31.99] = $18.20).

VOI Results

When we based our treatment choice decisions on duration of symptoms only, the baseline population value of perfect information was about $40 million and ranged from $13 million to $109 million over a wide range of threshold WTP values ($25 to $200 per day of avoided sinus congestion). This is driven by the fact that the chance that future information may change our current decision of using azithromycin extended release based on effectiveness results was only about 4 percent.

When costs of treatments were also considered for choosing between treatments, the value of future research on effectiveness maximized at around a threshold value of $50/day of avoided symptoms and amounted to $400 million. This was the threshold where the probability of current decision that azithromycin extended release was cost-effective reached 50 percent. Figure 2 presents the acceptability curve and the EVPI curve over a range of threshold WTP values. At the baseline threshold of $73, the expected value of future research was $250 million.

Conclusions

If treatment costs are not considered, the value of future research that can generate more precise estimates results on comparative time to symptom relief between azithromycin extended release versus amoxicillin/clavulanate in the treatment of acute sinusitis is low at any reasonable threshold value of cost per day of avoided symptom. This is because additional research is very unlikely to reverse the current conclusion that azithromycin provides more rapid resolution of symptoms. However, when treatment costs are considered, there is a substantial probability that azithromycin extended release is not cost-effective at current prices and that research to better clarify the most cost-effective treatment would be highly valuable. In addition, because the results used for this analysis come from a single study, an argument could be made additional studies even of outcomes if one believed that the results of this study might not be generalizable to other settings. For example, reasons for desiring additional studies besides the one used for this VOI analysis could include incomplete followup in the intervention and control groups (both 68–69%) that require a per-protocol rather than intention-to-treat analysis, the possibility that the epidemiology of sinusitis could differ in other settings.

Application 2: No survival modeling with survival effects from a randomized, controlled trial—the case of erlotinib and gemcitabine versus gemcitabine in pancreatic cancer

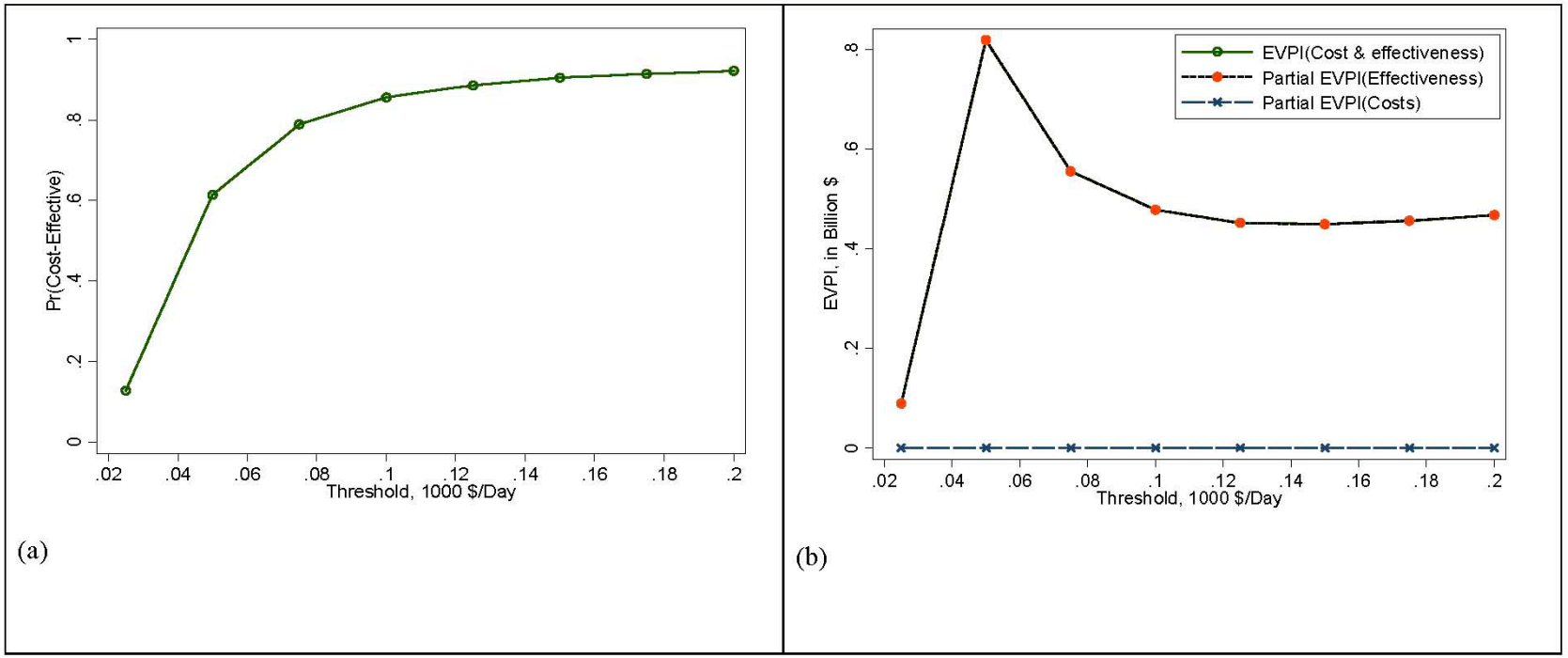
Background and Setting

Pancreatic cancer is the fourth most common cause of cancer death in the United States, with an estimated 38,000 new cases annually.[44] More than 90 percent of patients develop metastasis, and survival averages only 2 to 4 months in the absence of treatment.[45] Since 1997, gemcitabine has been the primary treatment for patients with metastatic pancreatic cancer. Recently, a Phase III trial documented a statistically significant improvement in survival with a combination of gemcitabine plus erlotinib compared to gemcitabine alone.[46]

Aims

We sought to assess the value of more precise information on the comparative effectiveness and cost-effectiveness of gemcitabine plus erlotinib compared to gemcitabine alone in patients with metastatic pancreatic cancer. These values will only be positive if future information can change treatment decisions. In this empirical analysis, we assume that current treatment choices are based on either current information on effectiveness (i.e., survival) or cost-effectiveness.

Figure 2. Acceptability curve and population expected value of perfect information (EVPI) curve for comparing azithromycin extended release versus amoxicillin/clavulanate in the treatment of acute sinusitis



Modeling of Health Outcomes, Approach to VOI Calculations, and Data

We used the published overall survival curves from the Phase III study to recover the individual level survival data under the two treatment arms. As a validation of this exercise, we were able to closely replicate the published data on the survival curve, the hazard ratio, and its significance using our individual level data. These are presented in Appendix C. Since almost all of the patients were followed until their death so that there was no difference in survival at the end of the study period, mean survival under each treatment was obtained by averaging the duration of survival over patients in each arm. One thousand bootstrap replicates of the individual-level data were used to generate the distribution of the mean survival under each arm. This distribution is shown in Appendix C. We emphasize that the approach to modeling survival here was directly based on the data from the clinical trial as opposed to modeling the progression of disease through health states and probability of death given health state as is typically done when a decision analysis model is used to model survival in a full-modeling approach to VOI.

A challenge in our analysis was the lack of information on variability in costs. To estimate EVPI for costs and effectiveness, we assumed a cost distribution in which the variance of the individual level costs under each treatment was proportional to the square of its mean. We used alternate distribution for costs (here we present results based on gamma distribution, but alternate results under a normal distribution were similar) maintaining this mean variance relationship. We estimated a distribution of mean costs arising out of a sample size similar to that of the Phase III trial.

Perspective, Incidence, Time Horizon, and Discounting

Our EVPI calculations were based on a prevalence of 35,000 patients and an annual incidence of 25,000 patients over a 5-year horizon, with incidence calculated based on an age-adjusted incidence rate of 11.7 per 100,000, an adult U.S. population of 75 percent if 310,000 and 92 percent of patients with pancreatic cancer presenting with advanced cancer.[47] We used a discount rate of 3 percent.

Cost-Effectiveness Results and Decisions Based on Current Information

Patients receiving gemcitabine plus erlotinib had a mean life expectancy of 0.69 years (SE=0.027) compared to 0.610 years (SE=0.026) for patients receiving gemcitabine alone. Based on information on effectiveness only, the current treatment decision that maximizes life expectancy is gemcitabine plus erlotinib. The annual cost (2010 U.S. dollars) of gemcitabine plus erlotinib therapy was estimated to be $29,238 while for gemcitabine alone was estimated to be $15,702.[48] Based on cost-effectiveness, current treatment decision should be the gemcitabine plus erlotinib only if the maximal threshold WTP for a year of life is above $180,000. Below that threshold, gemcitabine alone is the cost-effective treatment of choice.

VOI Results

When we based our treatment choice decisions on effectiveness only, the population value of perfect information was close to zero (<$10 million) over a wide range of threshold WTP values ($5K/Life year to $200K/Life year). This is because the chance that future information may

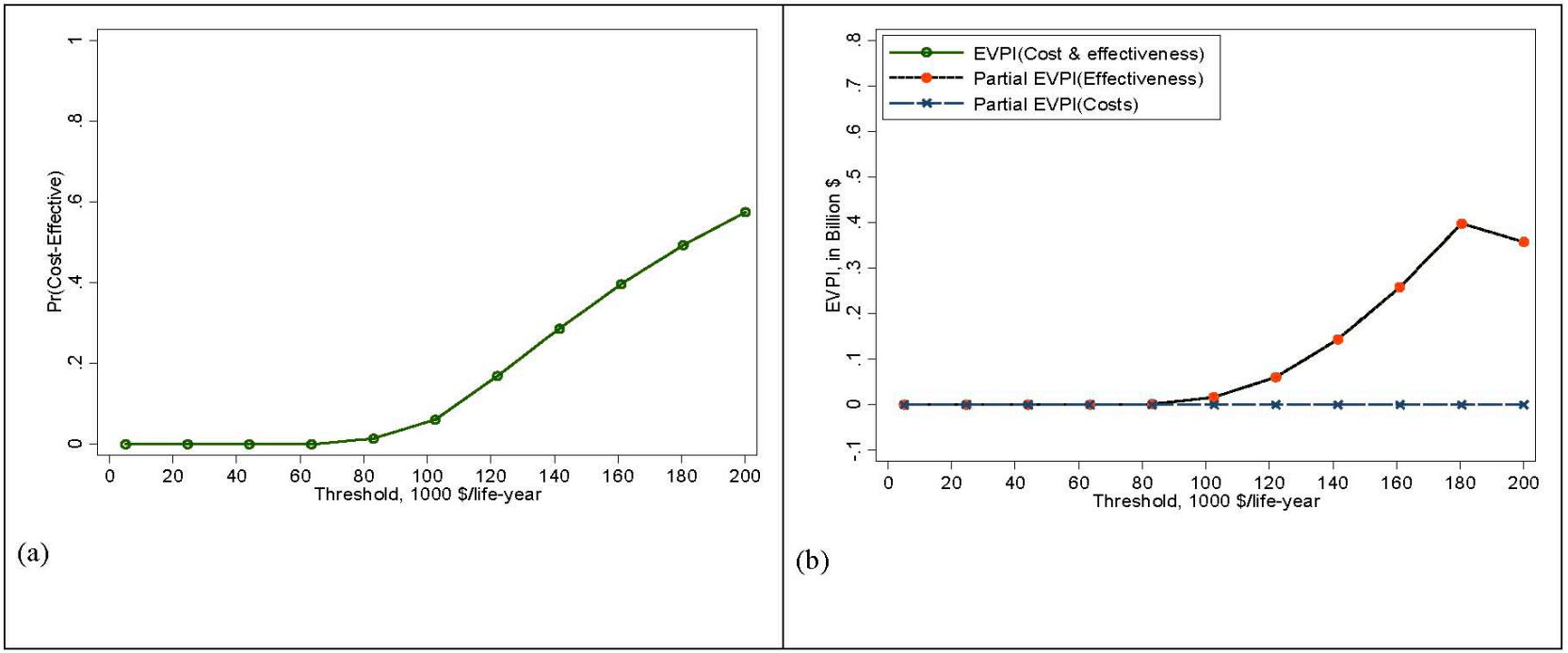
change our current decision of using gemcitabine plus erlotinib based on effectiveness results was less than 3 percent.

Figure 3 presents the acceptability curve and the EVPI curve over a range of threshold WTP values. As expected, at a WTP of $180,000 per QALY the probability that gemcitabine plus erlotinib is cost-effective compared to gemcitabine alone is 50 percent. This is also the WTP where the value of future research on more precise estimation of the comparative cost-effectiveness is maximized at about $400 million. When the WTP per QALY drops to $100,000 per QALY, the value of additional research is less than $20 million. Note that in this example, when treatment decisions are made based on cost-effectiveness, all of the future value of research is driven by the value of acquiring more precise information on effectiveness; information collected about costs could also have value and could change the value of additional information about effectiveness.

Conclusions

The value of future research that can generate more precise estimates results on comparative survival or costs between gemcitabine plus erlotinib versus gemcitabine alone in metastatic pancreatic cancer is low at any reasonable threshold value of cost per life year. This is because additional research is unlikely to change the current treatment decision recommended based on life expectancy. However, if the best treatment decision is based on cost-effectiveness, erlotinib plus gemcitabine is not cost-effective at WTP below $180,000 per QALY and gemcitabine alone is the preferred treatment. In this case, if the WTP threshold is sufficiently high, additional research on effectiveness could have an expected value as high as $400 million if the WTP per QALY is $180,000. However, if WTP is less than $100,000 per QALY, the value of research is less than $20 million, which may be too small compared to the cost of an additional clinical trial to justify the cost.

Figure 3. Acceptability curve and population expected value of perfect information (EVPI) curve for comparing gemcitabine plus erlotinib versus gemcitabine alone in the treatment of patients with metastatic pancreatic cancer



Conclusions

While the use of decision-analytic models to calculate the expected value of information is the dominant approach to the development of VOI methods to inform research priorities, minimal modeling approaches based on information on comprehensive health outcome measures can provide a less-demanding approach to performing VOI analysis. Our review of published VOI studies identified 17 applications of minimal modeling approaches in the academic literature and one in the grey literature. In addition, we performed two new minimal modeling VOI analyses. These two new minimal modeling VOI analyses each took only a day or two of work, as opposed to what we expect would be months for a typical full modeling approach to VOI.

Our results show that minimal modeling approaches can be readily applied in some circumstances and can provide evidence of vast variation in the value of research for different studies that can range from as little as $2 million to as much as $125 billion, a nearly 100,000-fold difference in value. The immense range of these estimates suggests that VOI analysis can provide insights into the value of research that may provide information that challenges and extends intuitive approaches to informing priorities for research. Our results also show that, as with full-modeling approaches to VOI, minimal modeling approaches demonstrate that VOI depends on the criteria used to define a decision, with very low VOI estimates if the gemcitabine decision is made only on the basis of health benefits, and much larger VOI if the decision is to be made also considering costs.

Our review and new analyses suggest several general situations in which minimal modeling approaches may be readily applicable. One of these approaches is when an intervention affects quality of life alone so that effects on survival do not need to be modeled (e.g., Meltzer [2009][7]). Another is when a study follows cohorts of patients randomized to the time of treatment from the time of treatment to death, recording all relevant outcomes (perhaps survival, quality of life, and costs at all points in time until death, ideally combined into net health benefit). Third, a study might collect comprehensive outcomes data from a trial in which survival is similar between two arms after some point, but survival or quality of life up to that point might differ. How often these criteria are met when considering specific research gaps is an empirical question, but it is clear that the data requirements will not be met in some circumstances so that minimal modeling approaches cannot fully substitute for full-modeling approaches to VOI.

Where the data needed for minimal modeling approaches to VOI is available, we found that simulation methods that use bootstrapping to address value of information have been most commonly used in the literature recently. To simplify such calculations for others, we have written a Stata command—evpi—that can be used to calculate expected value of information for conducting comparative effectiveness research for two treatments. One must specify as input a dataset that contains the empirical distribution of mean costs or effectiveness or both for each treatment. The command allows specification of the decisionmaking criteria (based on costs, effects, or cost-effectiveness), incidence, prevalence, time horizon of technology, discount rate, and the range of threshold values for willingness to pay for an effectiveness outcome. It provides options to draw both an acceptability curve and an expected VOI curve, as illustrated in Figures 2 and 3. The EVPI software is available from the authors on request, although we should note that development of this software is ongoing to extend its capability to include comparison of multiple treatments.

In addition to the significant data requirements of the approach we discuss, additional limitations of the minimal modeling framework should be noted. First, the above limitations imply that it will generally be impossible to apply the minimal modeling approach to VOI to study the value of research in interventions for chronic disease, since studies rarely follow outcomes fully to their final outcome. Full modeling approaches to VOI are likely more appropriate in those settings because of the tendency to rely on intermediate outcomes in clinical trials in chronic disease. Also, even when long-term trials are performed that measure comprehensive outcomes, their length and costs make the potential benefits of minimal modeling approaches in terms of speed and cost less important.

Second, the absence of a decision model makes it impossible to calculate the expected value of perfect partial information on specific parameters that may be partial determinants of the outcomes of the interventions being considered. One exception to this may be the separate effects of costs and outcomes. Not using decision models also means that the results of a VOI analysis cannot be tailored to a somewhat different clinical situation by the manipulation of the parameters of the model. Finally, the minimal modeling approach is limited by the fact that many cutting-edge areas of medical technology may have not prior data with which to inform a minimal modeling approach. Cases such as these may require the use of full modeling approaches to develop meaningful estimates of the value of research.

Nevertheless, when the minimal modeling approach is feasible, its advantages are potentially important in allowing VOI analyses to be done in situations where the cost of doing a study would be too small to justify spending significant spending on a VOI analysis. One example of this would be where the study considered might be the performance of a systematic review. Similarly, a minimal modeling approach might be useful when a full modeling approach might have certain advantages but the expertise to perform a full modeling approach simply is not available. Other examples might be when the results of a VOI analysis were required very quickly, such as when a decision must be made about funding a clinical trial or continuing one already in progress. The latter case also reinforces the argument made above that minimal modeling VOI may be of use in the context of adaptive clinical trials, because the data collected at each stage of an adaptive trial can provide data for a minimal modeling approach that can be rapidly used to inform subsequent stages of the trial. Indeed, in cases of new technologies where no prior data is available, appreciation of the minimal modeling approach may provide rationale for an initial small and underpowered trial as the first step in a potentially larger adaptive trial, with later design decisions specified based on the results of the subsequent VOI analyses.

Finally, it should be noted that resources invested in value of information analysis could, at least hypothetically, also be invested in directly seeking to answer clinical research questions rather than choosing which clinical research questions to answer. This is a real tradeoff; it is surely possible that investments in VOI might have lower returns than investments in other types of research. However, the range of value of research estimates we report above—from as little as $2 million to as much as $125 billion—suggests that when a minimal modeling approach to VOI can be applied, the several days of work involved seem likely to be well spent if they even rarely cause changes in research priorities that are for the better.

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Appendix A. Details of Application 1 and Application 2

Table A1. Details of application 1 (azithromycin vs. amoxicillin/clavulanate in acute bacterial sinusitis) and application 2 (erlotinib and gemcitabine vs. gemcitabine alone in pancreatic cancer)

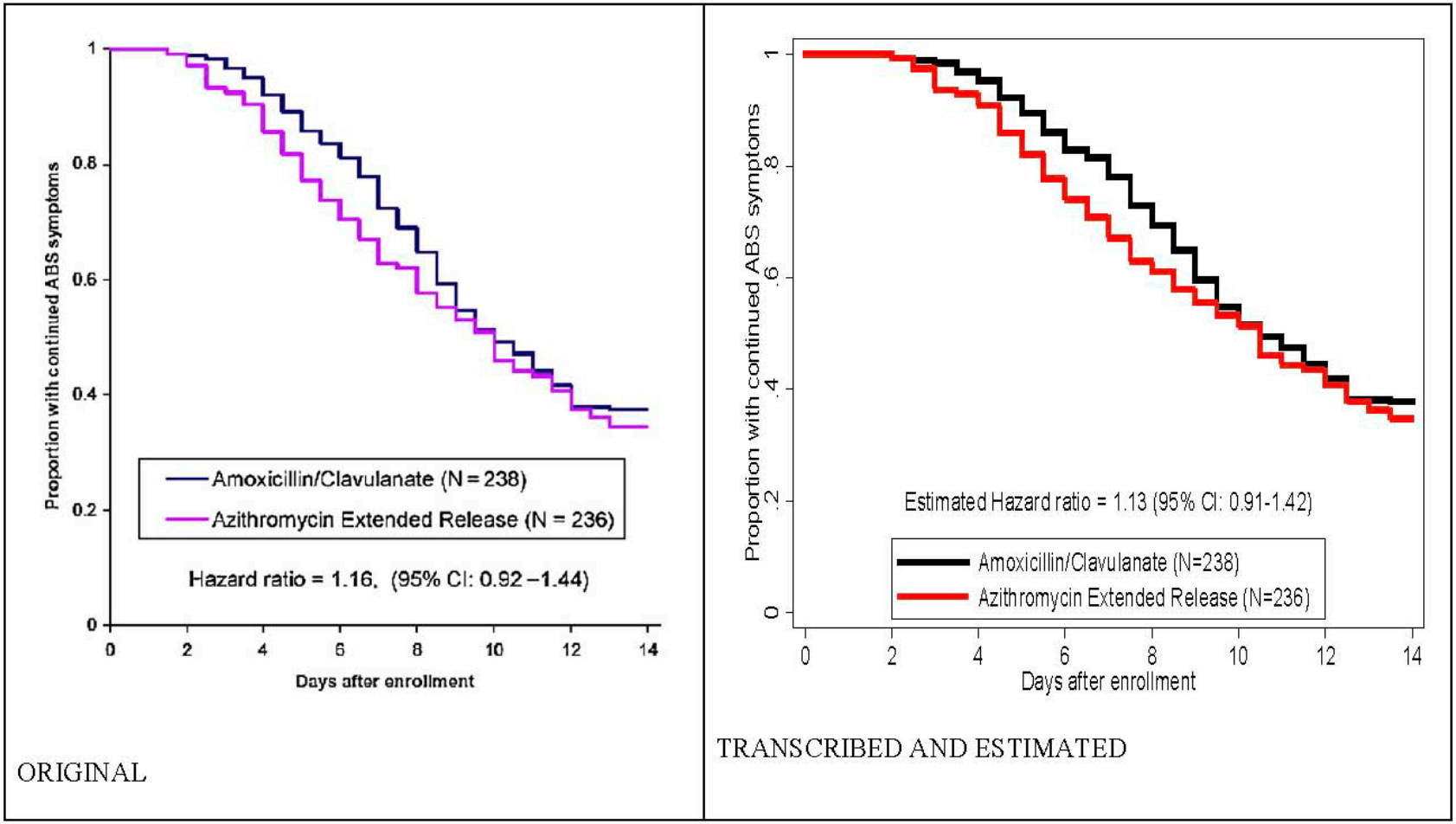
Application	Application 1: Azithromycin vs. Amoxicillin/Clavulanate in Acute Bacterial Sinusitis	Application 2: Erlotinib and Gemcitabine vs. Gemcitabine Alone in Pancreatic Cancer
Modeling of health outcomes (i.e. limited modeling component)	No modeling, manual replication of curve for symptom relief	No modeling, manual replication of survival curve
Approach to value of information calculations	Bootstrapping/simulation, nonparametric	Bootstrapping/simulation, nonparametric
Application	Azithromycin vs. amoxicillin/clavulanate in patients with acute bacterial sinusitis	Erlotinib and gemcitabine vs. gemcitabine in patients with pancreatic cancer
Setting	U.S.	U.S.
Perspective	Third-party payer	Third-party payer
Data	-Symptom resolution: Comparative effectiveness study [41] -Drug price: Drug Topics Red Book (42)	-Survival curves: Phase III trial (46) - Costs: assumptions
Incidence [prevalence]	10M	25k [35k]
Time horizon	10 years	5 year
Discounting	3%	3%
(Cost-)effectiveness results	- Effectiveness = -0.57 days to symptom resolution - NB: $18.2	- Effectiveness = +0.08 life-years - ICER~$180,000/life-year
Value of information results	Effects only: pEVPI = $40M Both cost and effects: pEVPI =$250M	Effects only: pEVPI = $0 Both cost and effects: pEVPI = $400M
Willingness-to-pay	WTP = $73.20/day to symptom resolution	WTP = $180k/life-year

NB = net benefit; pEVPI = population expected value of information; WTP = willingness-to-pay

Brief description of the methods use to develop the survival curves in the two examples: After enlarging a hard copy of the published survival figure, we drew a rectangular grid of lines on the figure in order to read the treatment-specific survival fraction corresponding to each unit increment of time (a day for the sinusitis example [Appendix B] and a half-month for the pancreatic cancer example [Appendix C]). We then took an empty dataset with *n* observations, *n* corresponding to the treatment-specific sample sizes of the respective study, and assigned a time of event to each observation (representing one patient) based on the survival fraction and the corresponding time, thereby generating an individual level outcomes dataset. We validated this approach by replicating the point estimate of the hazard ratio reported in the original analysis using our generated individual-level data. We also performed a nonparametric bootstrap of the individual level data to replicate the 95 percent confidence interval of the hazard ratio reported in the original analyses. These results are presented in Appendix B and Appendix C. These bootstrap results also produced the distribution of comparative effects that we use for the value of information analyses.

Appendix B. Curves for Symptom Resolution

Figure B1. Curves for symptom resolution in azithromycin extended release versus amoxicillin/clavulanate in acute sinusitis



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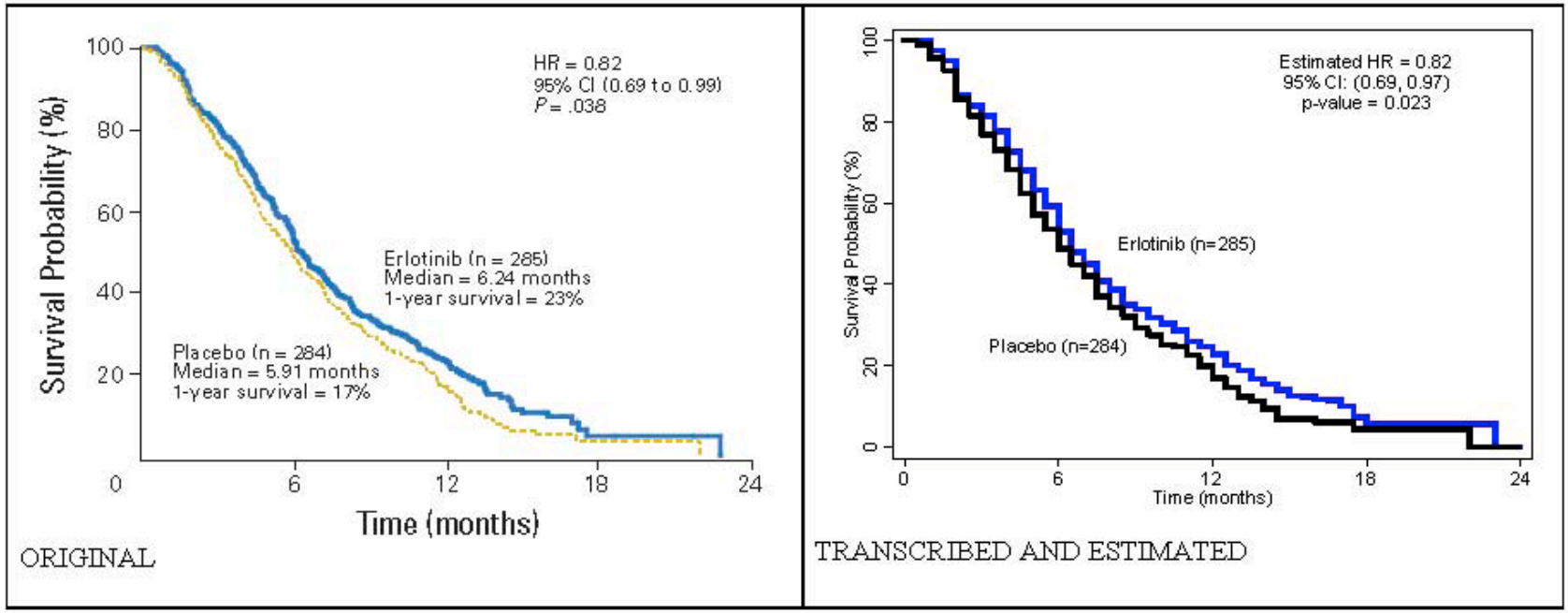
Appendix C. Survival Curves

Figure C1. Survival curves for gemcitabine plus erlotinib versus gemcitabine alone in metastatic pancreatic cancer



 Moore MJ, et al. J Clin Oncol 2007;(25):1960–66.[46]