Interpretation of the expected value of perfect information and research recommendations: a systematic review and empirical investigation

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Introduction

The move towards evidence-based decision making has highlighted the importance of rigorous information on the value of health care services and has contributed to an increase in the demand for clinical research [1, 2]. At the same time, the public budget for research is limited and funding organisations such as the National Institute for Health Research in the UK and the National Institutes of Health in the US have to make cost-effective choices on which research projects to prioritise and fund. [3-5] Allocating funds to research represents an investment of scarce public resources, and this has given rise to calls for funding decisions to be informed by explicit evidence on the value of research proposals. [6-12]

A formal framework, with roots in statistical decision theory [13], has been proposed to assess the value of information (VOI) to a decision maker in health care. [14, 15] A key VOI measure is the 'expected value of perfect information' (EVPI), which represents the monetary value that can be attached to completely eliminating uncertainty in the decision-making process. The EVPI value for an individual is defined as the difference between the value associated with a decision made on the basis of current information, and the value that could be expected if perfect information were available on which a decision could be based. [16] However, a more appropriate comparative measure for the value of acquiring further information is the population EVPI, which takes into account the number of people who may benefit from the additional research by incorporating measures of both the time frame over which the information is expected to retain its usefulness (before, for example, newer technologies render the intervention obsolete), and the number of people with the condition.

EVPI has the potential to be used as a means of assessing research priorities in a funds-limited research environment. [17] If the cost of obtaining further information (via a randomised controlled trial (RCT), for example) exceeds the EVPI, there is little justification for proceeding with research, and a decision maker can be confident that they could not make a better decision by waiting. Thus the EVPI

exceeding the cost of running a trial is a necessary condition that must be fulfilled before research can be considered potentially worthwhile and represents a maximum amount that a rational decision maker should spend on further research. [18] It should be noted that a high EVPI value is not a sufficient condition for advising further research, and firm recommendations in favour of further research based on the EVPI value alone are inappropriate. More information from expected value of sample information (EVSI) studies is required to determine whether a particular piece of research should be conducted. [19] However, a recent review of EVI methods and applications found that, despite EVSI being the metric of choice for informing decision making, applied calculations are rarer than applied EVPI values. [20] It is likely that this imbalance arises because EVSI is both conceptually and computationally complex, while EVPI analysis is relatively straightforward to conduct. Given that different trials are anticipated to cost different amounts, and the measure that should strictly be used to distinguish between those trials worth funding is EVSI, it is possible to see different recommendations for similar values of EVPI. For example, Forbes *et al* recommended further research on the basis of an EVPI value of £10.7 million [21], whilst Rogowski *et al* did not recommend further research with an EVPI value of £10.76 million. [22] It is also likely that considerations other than the magnitude of EVPI (e.g. disease area of interest, type of outcome used etc.) may be taken into account in making research recommendations.

With this in mind, we conducted a systematic literature review to identify applied VoI studies with the aim of investigating how researchers interpret calculated EVPI values when making research recommendations. The study explores whether there exists an empirical magnitude of EVPI below which no recommendation for further health research is typically made (*i.e.* whether there is an empirical threshold), looks into the degree of consistency across the literature in the recommendations for further research for a given level of EVPI, and investigates whether different factors, including disease area, country and measure of outcome, may influence recommendations. We aim to observe what is happening in practice, in order to improve transparency in discussions around decision making.

Methods

The review was carried out in line with widely used recommendations for undertaking systematic literature reviews [23] and aimed to retrieve applied studies reporting EVPI calculations. Prior to the publication of the methodological description by Claxton and Posnett in 1996 [14], EVPI calculations were rarely reported in health economics; therefore, conducting the search from 1990 covers the probable extent of relevant literature. From April 2011, the Cancer Drugs Fund came into force in England [24]; this altered commissioning attitudes to the acceptable threshold for funding particular cancer treatments, and therefore has the potential to alter approaches to funding research. Therefore, the period searched was limited to 1990 to 2010 to avoid adding complications to possible interpretations.

Search strategy

As EVPI calculations are not routinely reported in abstracts and keywords, two different approaches to searching the literature were followed. In the first, standard bibliographic databases were searched with relatively broad search terms, whilst in the second, full-text searching was performed with tightly defined search terms. The bibliographic databases Medline, EMBASE, CINAHL, Web of Science and The Cochrane Library (which includes the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, and the NHS Economic Evaluation Database) were searched using a combination of search terms and wildcards to cover the range of different value of information phrases. Adding the qualifier “AND cost” significantly improved the specificity of the searches without reducing the sensitivity. Full-text searching was undertaken via the websites of the journal publishers and suppliers AdisOnline, HighWire Press, IngentaConnect, Cambridge Journals Online, ScienceDirect and the UK Health Technology Assessment (HTA) site, covering the significant journals in health economics. Full-text searches were also conducted using the Google Scholar search engine. Details of the searches undertaken are given in Appendix 1 (online).

Inclusion criteria

Articles were included if they: reported calculations of one or more measures of the population expected value of perfect information; were undertaken as part of an applied study assessing health care interventions; were peer-reviewed publications . Articles were excluded if: the EVPI calculation was carried out purely to illustrate a methodological point (for example, if the data used were manipulated to disguise their origin); the intervention was an environmental health application; the article was not written in English.

Selection process

Abstracts of identified studies were screened by one author (JT). A 10 percent sample of the abstracts was screened by two reviewers (LA and JT) to check for accuracy and consistency; disagreements were resolved by discussion. Some articles without EVPI calculations were eliminated by consulting health economic assessments in the NHS Economic Evaluation Database (EED) or contacting the author.

For the remaining abstracts, full-text versions were obtained and screened electronically (by JT) where possible. Multiple pdf file search functionality was used to search for the word 'perfect' in order to eliminate articles that would not contain an EVPI calculation. Non-searchable pdfs were identified, and these articles were manually scanned for EVPI calculations. For articles containing the word 'perfect', the context was examined to eliminate irrelevant material. A second screening cycle was applied to those articles that either did not contain the word 'perfect' or contained it in an irrelevant context by searching for the word 'information'.

A final screening process was undertaken by reading the full text and eliminating articles that did not describe an applied EVPI calculation. Some studies were reported twice; only the most recently published article was included to maximise the likelihood of a full report. However, the earlier report was used to supply additional details where necessary.

Data extraction

For each study that met the inclusion criteria, extracted information included background characteristics such as publication year, funder, location and disease group based on ICD-10 chapter

heading. Both individual and population EVPI values were extracted, along with the willingness-to-pay (WTP) threshold (*i.e.* the hypothetical value that society is willing to pay for an additional unit of health outcome), outcome measure and currency. The time frame over which the technology was expected to be useful was also noted. Where multiple EVPI values were cited, a pragmatic approach to choosing a single value was taken; for example, a value at a WTP of £30,000 (or other commonly cited WTP values) was taken where possible, and EVPI values were read from graphs if necessary. Finally, brief text excerpts describing the interpretation of the values, recommendations based on the values and research prioritisation comments were extracted verbatim.

The extracted texts were classified according to whether the recommendation was for or against further research (*i.e.* positive or negative), on an ordinal scale of recommendations. The scale ran from 'beneficial' to do further research (for example, if the technique was said to warrant further research or further research was justified), through 'probably beneficial' (*e.g.* if further research was considered likely to be worthwhile), 'possibly beneficial' (if phrases such as 'could be cost-effective' were used), 'possibly not beneficial' (if research 'may not be' cost-effective, for example), 'probably not beneficial' (for example, if research was considered unlikely to represent an efficient use of resources) to 'not beneficial' to do further research (*e.g.* if it was stated that research would not be justified).

Extracted data were used to classify the type of research funder. Population EVPI and WTP values were converted to sterling using Bank of England exchange rates, taking the value at 31 December (or closest preceding day) of the relevant cost year of the study, or the publication year if unavailable. [25] Owing to the complex nature of EVPI calculations with costs bound up in WTP thresholds, and the lack of consistent reporting of cost year, it was not possible to convert EVPI values to a common cost year. The quality of the articles was not formally assessed and did not form one of the exclusion criteria because we were interested in how authors responded to the values that they found rather than whether the EVPI calculations were correctly derived. Therefore, articles with methodological limitations were not excluded on that basis alone. For example, where an inappropriately large population had been used to derive a population EVPI resulting in a hugely inflated value, the study was included in the analysis because a recommendation was still made and flowed logically from the value calculated.

Statistical modelling

Extracted data provided the basis for exploring possible relationships between authors' research recommendations and various factors, such as country that the study relates to, study funder, disease area, year of publication and magnitude of EVPI. As a first step, we used the data to consider graphically how these factors may affect research recommendations. In addition, the impact of these factors on the dichotomous 'recommend/not recommend' outcome variable was explored using logistic regression. Briefly, logistic regression models the effect of one or more explanatory variables and interaction terms (here, various factors) on the odds of a dichotomous dependent variable (here, recommend/not recommend). Different interaction terms were considered on the premise that these have a plausible modifying effect on the outcome variable (e.g. interaction between EVPI and country, assuming that EVPI may differ according to the country that research relates to). Different model specifications were considered using stepwise selection (forward selection and stepwise elimination) and hierarchical regression. An unrestricted (full) model containing all the available variables was compared to several nested models using the likelihood ratio (LR) test and the Akaike (AIC) and Bayesian (BIC) information criteria. [26] An empirical threshold EVPI value was calculated at the point where the probability of a positive recommendation is 0.5, holding any covariates in the model fixed at their baseline values. [27] Statistical and graphical analyses were performed using Stata 11. [28]

Results

The bibliographic database searches identified 2078 potentially relevant articles, while a further 560 articles were identified via full-text searches. Following deduplication, 2497 abstracts required screening. Screening by two reviewers of a 10% sample (250 abstracts) resulted in good agreement on inclusion ($\kappa = 0.72$). Inspection of the abstracts, consultation of the NHS EED and author contacts led to 2032 articles being eliminated from consideration, including 13 articles that were written in a language other than English.

Full-text versions of 465 articles were obtained, and 322 were eliminated electronically or by scanning hard copies. The remaining 143 articles underwent a close reading of the full text, and data extraction was undertaken for 86 articles, listed in Appendix 2 (online). Extracted data are presented in Appendix 3 (online). A flowchart describing the systematic review process is given in Figure 1.

Background characteristics

The publications included were drawn from a wide range of journals. Higher numbers of EVPI calculations have been observed in recent years. Nine studies were carried out alongside trials, with the remainder being pure modelling studies. Where stated, time frames over which the technology under study was expected to remain useful varied from one to 30 years, with 38 out of 86 studies opting for 10 years. WTP thresholds for quality-adjusted life year (QALY) outcomes ranged from £500 to nearly £80,000. Seven articles reported EVSI calculations in addition to EVPI results. Other key characteristics of the included studies are listed in Table 1.

Research recommendations

Categorical recommendations were rare, with only a few explicitly using the term ‘recommend’; however, many were implicit. Where an absolute, rather than a comparative, value judgment was applied, the EVPI was described as ‘low’, ‘small’, ‘high’, ‘large’ or ‘substantial’. Of the 86 included articles, 13 suggested no further research, whilst 66 were more positive (10 implicitly through parameter research recommendations, two on the basis of factors other than VoI results and the remainder on the basis of the EVPI value). Seven made no recommendation. The costs of carrying out research—an essential requirement for making a robust recommendation—were not frequently assessed with few articles making reference to actual figures. These estimates varied substantially (for example, as low as €200,000 (£172,000) and as high as $27.1 million (£17.5 million) for a phase III clinical trial), as might be expected for varying trial designs and settings.

The classification of recommendations is illustrated in Figure 2. Owing to the extensive range of EVPI values observed, the graphs are plotted on a natural logarithmic scale. For presentation purposes, the scale has been truncated and study numbers are omitted. The graph indicates that stronger belief that no further research should be pursued is clustered at lower EVPI values, while a strong belief that research should be carried out tends to be more common towards higher EVPI values. Collapsing the data into binary categories of no further research (including all three negative categories) and any other recommendation (Figure 3), suggests a cut-off point around an EVPI value of £250,000 below which research was not typically recommended. Between £250,000 and £2 million, recommendations

were variable, while EVPI values over £2 million did not typically attract recommendations against further research.

Statistical analysis

The statistical analysis showed EVPI to be the only significant predictor (p=0.007) of research recommendations. No interaction terms were found to be significant at the 0.05 level. A restricted model containing EVPI as the only explanatory variable ('EVPI only') fitted the data significantly better than a constant-only (empty) model (Likelihood ratio: 37.8; p<0.000). The unrestricted model containing all the available variables ('full' model) achieved a small, non-significant improvement in explanatory strength over the 'EVPI only' model (Likelihood ratio: 40.85, p=0.723). Stepwise selection also resulted in a model with EVPI as the only statistically significant parameter at significance levels up to 0.15.

Results of the 'EVPI only' and 'full' models, in terms of changes in odds of a positive recommendation for a unit change in each explanatory variable are given in Table 2. In the 'EVPI only' model, an increase in EVPI by £1 million is associated with an increase in the odds of a positive research recommendation by 56% (95% CI: 13% to 115%, p=0.007). Predicted values of the probability of a positive recommendation at different values of EVPI are shown in Figure 4. At levels of EVPI up to £1.48 million, the probability of a study recommending research is less than 0.5. At £1.48 million, the probability of a positive recommendation reaches 0.5 (95% CI: 0.29 to 0.70), indicating that a threshold value above (below) which researchers are more (less) likely to recommend research exists roughly at £1.5 million. For EVPI values between £1.5 and £4 million, the probability is between 50% and 75%, while for higher EVPI values, in excess of £10 million, this probability is over 95%. While not statistically significant, the odds of a positive recommendation as calculated using the 'full' model were higher for studies on neoplasms, and studies funded by academic institutions and the industry compared to those sponsored by the government or medical charities. The odds of a positive recommendation were lower for studies the results of which relate to the UK, for studies that report QALYs and for studies published after 2007 (Appendix 4 online). Given that none of these variables were statistically significant predictors of the probability of a positive recommendation, we emphasise the discussion on the findings of the 'full' model is intended to provide indications, rather than firm conclusions.

Discussion

Our exploration suggests that recommendations are reasonably consistent with EVPI values, with greater EVPI values attracting more positive recommendations for research. An empirical threshold value of £1.48 million was determined via a statistical analysis, above which the predicted likelihood of a positive recommendation exceeds 0.5. The use of an EVPI value alone to make an explicit firm recommendation to conduct further research would however be inappropriate; most positive recommendations also took other factors into account, expressing the recommendation in terms of possible, rather than definite, benefits.

Different factors may have a bearing on the interpretation of EVPI and subsequent recommendations, although none were found to be statistically significant in this study. Neoplasms appear to attract a higher rate of positive research recommendations than other disease areas, which could mirror societal factors; cancers are overrepresented in the media compared with other diseases [29] and societal interest in, and approval for, cancer research may influence authors. In the top ten therapeutic research areas focused on by pharmaceutical companies, cancer drugs outweigh other areas by a factor of at least 2.5 [30]; cancer research is well supported by multiple funding sources including charitable entities [31], and authors may be encouraged to make positive research recommendations by the likelihood of receiving research funding. Funding by industry sponsors is associated with the presentation of more positive cost-effectiveness results, a form of publication bias. [32] This study suggests that industry sponsors may be more likely than government sponsors to make positive recommendations based on their VoI results, which may tally well with commercial interests. However, academic sponsors were also more likely than government sponsors to make positive recommendations. Studies published before 2007 are more likely to give positive recommendations, which could be as a result of a more cautious stance towards recommending research in a period characterised by policies aimed to contain public expenditure. Although there is a possibility that researchers naturally have a vested interest in recommending further research, this study does not provide any significant evidence to support this idea. Most of the identified studies were carried out with a view to informing treatment and research recommendations in the UK. The preponderance of studies originating from the UK is likely to have arisen as a result of national

guidelines, with NICE having formally advocated the use of VoI methods in England and Wales in 2004. [33]

As Eckermann *et al* [34] point out, in determining a threshold value of EVPI one needs to consider the costs of undertaking research, which, in turn, depends on the type and size of the proposed research programme. The costs of further research can vary significantly. In 2005, clinical trials cost a total of $24 billion in the US, representing a mean cost of just under £3 million per trial [35], while in the UK £950 million was spent, at an average of approximately £100,000 per trial. [36] However, the reasoning behind making a particular recommendation was rarely related to the actual costs of carrying out research, with few studies explicitly citing these costs. One paper referred to the expected high costs of running a trial in that particular disease area and the authors were negative about further research even with a relatively high EVPI value of £10.76 million [22]; the authors also took into account the fact that the drug was likely to come off patent during any trial. Costs that were cited covered a broad range, indicating that there is substantial variability around the estimates of trial costs. However, although not explicitly mentioned, the observed values at which research is typically recommended correspond reasonably well with average costs of running trials; it appears that authors implicitly acknowledge probable trial costs. The region of uncertainty between £250,000 and £2 million, where recommendations were not consistent, very plausibly covers typical trial costs. This potential variation in trial costs means that the 'threshold' we have identified cannot be extrapolated to be treated as a rule that should be followed in all cases.

The study has both strengths and weaknesses. It represents the first attempt at deriving an empirical 'threshold' value of EVPI. The search strategy was rigorous and thorough in order to identify the applied VoI literature. Owing to the variable quality of the suppliers' boolean logic implementations, and the restriction to English language articles only, some relevant material may have been overlooked; however, this is not likely to alter the broad conclusions. Material from the grey literature was not sought and this may have led to the omission of some relevant material. It is not clear whether grey material is more or less likely to influence decision making. However, as the interpretation of EVPI values in terms of further recommendations for research is at the discretion of the researcher, we do not believe it is likely that there is a systematic reason for EVPI values to appear in the grey literature only. The texts examined covered a range of countries and cost years.

EVPI values were converted to a common currency but not to a common cost year, which may have affected the observed threshold. However, we do not believe that this limitation would have had a substantial effect on the outcome; recommendations against further research were drawn from a wide range of years, and publication year did not have a significant effect on the likelihood of recommendation. Inevitably, there was a level of subjectivity in the classification schema for the recommendations, and also in the decision of which EVPI value to choose when multiple values were given.

Conclusions

Empirical analysis on the basis of the identified literature suggests that calculated EVPI values are a key driver of researchers' recommendations for further research. Factors other than EVPI, including disease area, funder, study location, publication year and outcome reported, may have a bearing on recommendations for further research, however none of them reached statistical significance in the analysis. A threshold EVPI value above which the predicted probability of a positive recommendation exceeds 0.5 was found to be around £1.48 million, though there is much variation around this value.

EVPI should not be seen as a substitute for EVSI, which is a more realistic and informative measure of the value of pursuing 'real-world' sample research. However, we believe that there is a role for EVPI in research prioritisation, in providing a simple criterion which can indicate the situations where pursuing further research would be wasteful.

This study offers insights into factors and considerations that may affect recommendations made in light of EVPI values. Unless such factors and considerations are understood and made explicit, there will always be a risk that researchers' recommendations for further studies will be treated as subjective and opaque.

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Table 1. Characteristics of the 86 included studies

Characteristic		Number (%)
Funder		
	Government	53 (61.6)
	Industry-related	17 (19.8)
	Academic	14 (16.3)
	Charity	2 (2.3)
Disease group		
	Circulatory system	20 (23.3)
	Neoplasms	19 (22.1)
	Musculoskeletal system	8 (9.3)
	Genitourinary system	5 (5.8)
	Other	34 (39.5)
Outcome measure		
	QALYs	74 (86.0)
	Life-years gained	7 (8.1)
	Other	5 (5.8)
Currency		
	Sterling	48 (53.5)
	US$	16 (18.6)
	Euros	13 (15.1)
	Can$	6 (7.0)
	Other	3 (3.5)
Location		
	UK	46 (53.5)
	US	13 (15.1)
	Netherlands	12 (14.0)
	Canada	6 (7.0)
	Other	9 (10.5)
Publication date		
	2000–2005	12 (14.0)
	2006–2010	74 (86.0)

Table 2. Results of 'EVPI only' and 'full' models

Model	Predictor variables	Odds ratio	SE	P>|z|	95% Confidence interval		Likelihood ratio	McFadden's adjusted R^2	Pr>LR	Akaike Information Criterion	Bayesian Information Criterion
EVPI only	EVPI	1.558	0.254	0.007	1.131	2.145	37.8	0.463	0.000	0.456	-33.34
Full model	EVPI	1.679	0.329	0.008	1.143	2.466	39.85	0.176	0.723	0.700	-5.22
	Neoplasms	1.866	2.072	0.574	0.212	16.442					
	Funder (base category: government/charity)										
	Industry	1.431	2.603	0.844	0.040	50.601					
	Academia	4.549	7.143	0.335	0.210	98.746					
	United Kingdom	0.442	0.472	0.444	0.055	3.579					
	QALYs	0.713	0.842	0.775	0.070	7.217					
	Publication year (base categ. 'before 2007')										
	2007-2008	0.689	0.836	0.759	0.064	7.428					
	2009-2010	0.286	0.349	0.305	0.026	3.133					
Statistic testing the null hypothesis that the addition of variables does not contribute to improved explanatory power (ie. increased values of log-likelihood)											

Figure 1. Flowchart

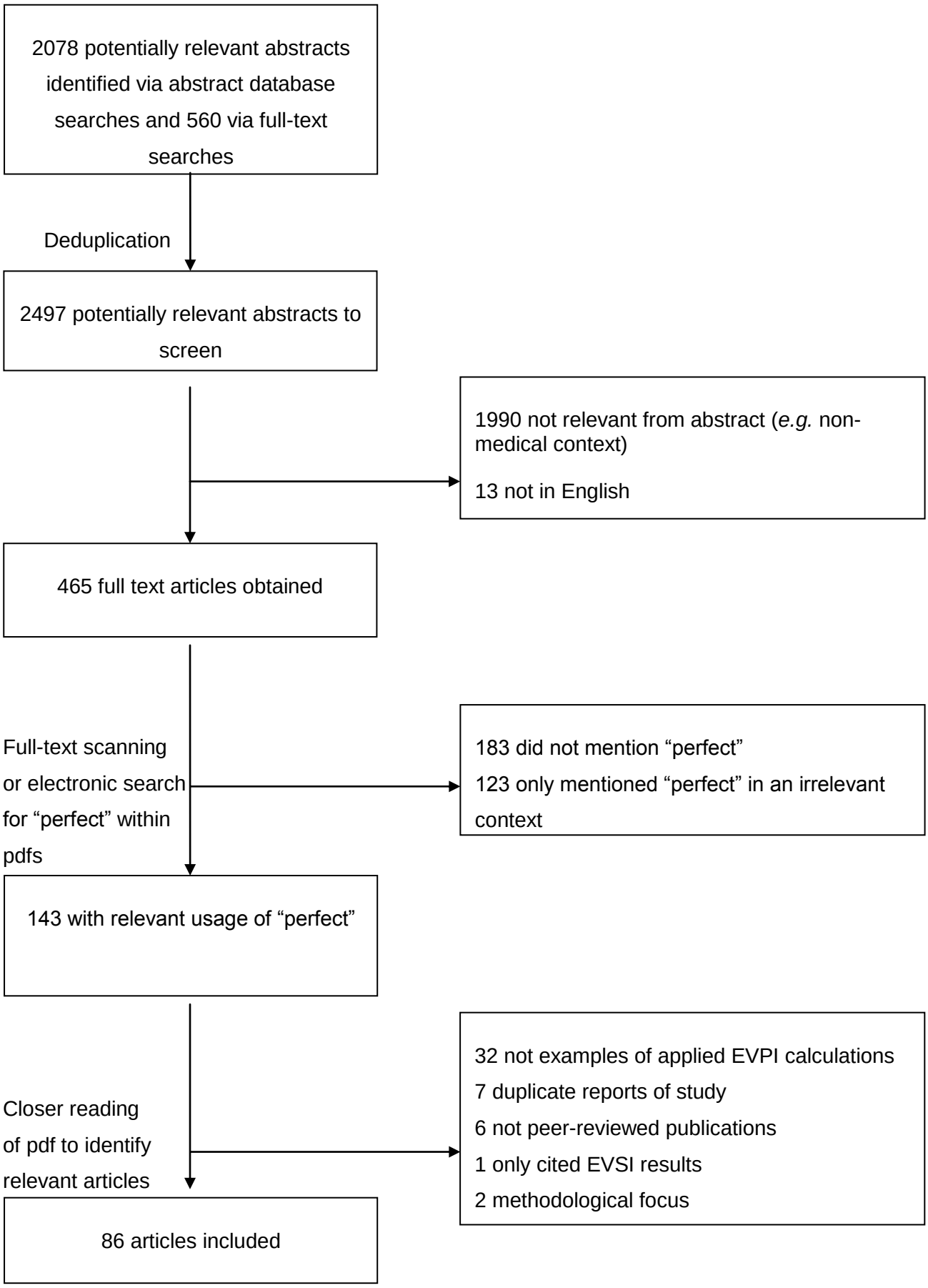


Figure 2. Recommendations for further research by EVPI value; values are plotted on a log scale.

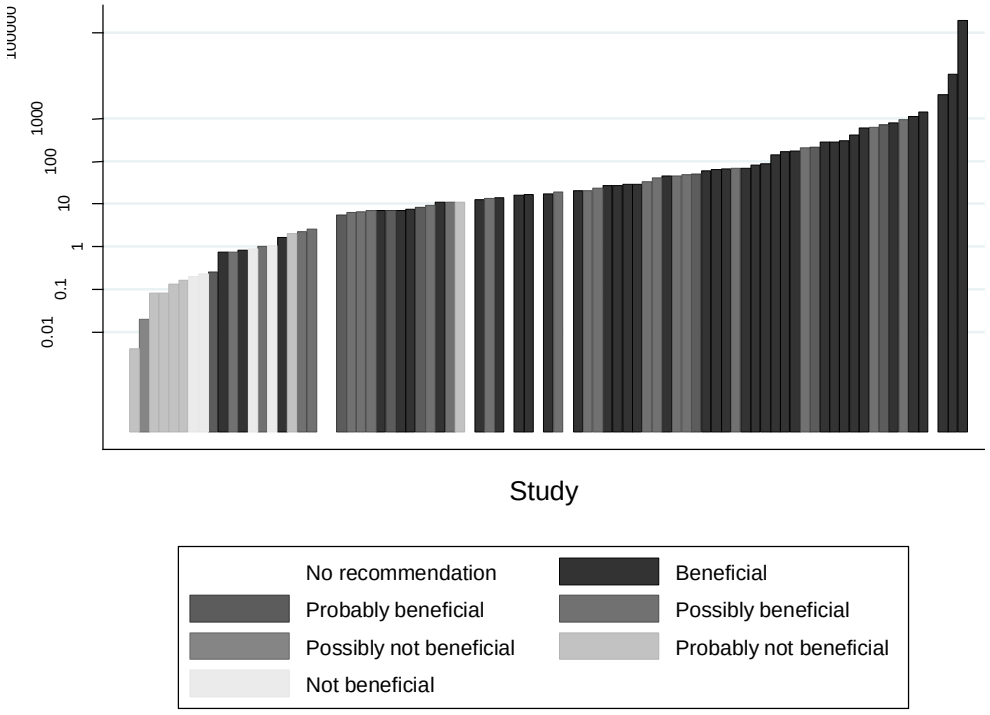


Figure 3. Recommendations for further research collapsed into binary ‘no further research’ versus any other recommendation; values are plotted on a log scale.

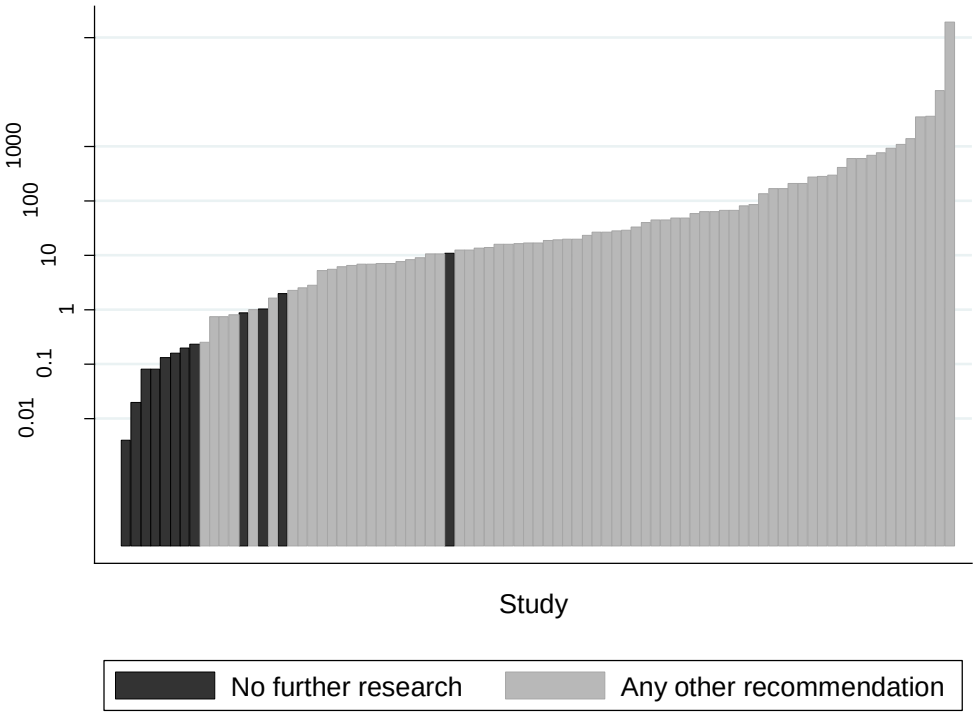
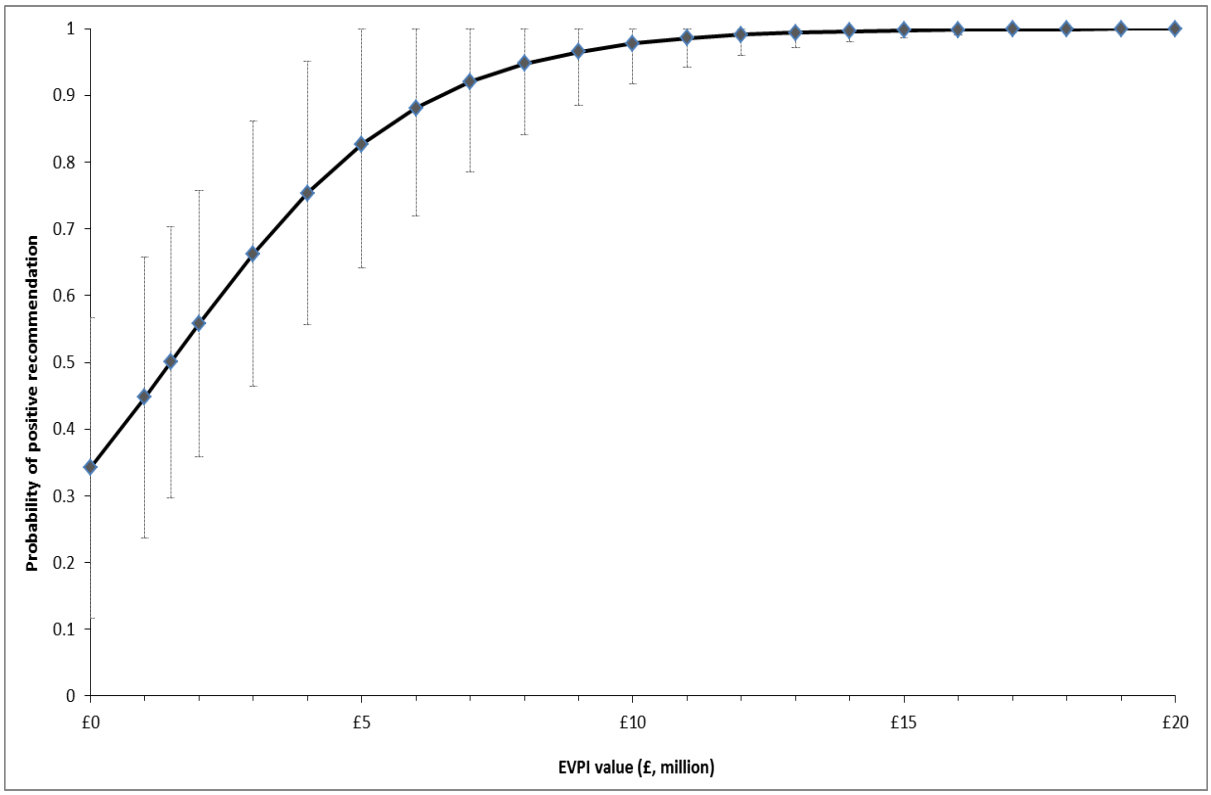


Figure 4. Predicted probability of positive recommendation at different EVPI values obtained from 'EVPI only' model.



Appendix 1. Systematic searches performed

Bibliographic database searches

Medline (29 July 2011, 1990-2010, lemmatization on, via Web of Knowledge)

Search number	Search	No. of results
#1	Topic=(cost)	254034
#2	Topic=("Value of information")	253
#3	Topic=("Value of * information")	370
#4	Topic=("Value of * * information")	131
#5	Topic=(EVPI*)	31
#6	#5 OR #4 OR #3 OR #2	677
#7	#6 AND #1	220
#8	MeSH Heading=(Cost benefit analysis)	42894
#9	MeSH Heading:exp=(Decision making)	78616
#10	MeSH Heading:exp=(Decision support techniques)	45358
#11	MeSH Heading:exp=(Decision theory)	7726
#12	MeSH Heading:exp=(Decision trees)	7254
#13	MeSH Heading=(Models econometric)	3333
#14	MeSH Heading=(Models economic)	4134
#15	MeSH Heading=(Models statistical)	49631
#16	MeSH Heading:exp=(Health care rationing)	8483
#17	MeSH Heading:exp=(Health care costs)	36673
#18	MeSH Heading:exp=(Health priorities)	6766
#19	MeSH Heading:exp=(Health policy)	60902
#20	MeSH Heading=(Economics Medical)	2276
#21	MeSH Heading:exp=(Markov chains)	6650
#22	MeSH Heading:exp=(Uncertainty)	3709
#23	MeSH Heading:exp=(Delivery of health care)	534223

#24	#23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8	731008
#25	Topic=("perfect information")	99
#26	Topic=(value of information)	57807
#27	#26 OR #25	57833
#28	#27 AND #24 AND #1	1772
#29	#28 OR #7	1819

Web of Science (29 July 2011, 1990-2010, lemmatization on, via Web of Knowledge)

Search number	Search	No. of results
# 1	Topic=("value of information")	898
# 2	Topic=("value of * information")	756
# 3	Topic=("value of * * information")	338
# 4	Topic=(EVPI*)	48
# 5	Topic=(cost)	441108
# 6	#4 OR #3 OR #2 OR #1	1790
# 7	#6 AND #5	511
# 8	#6 AND #5 Refined by: [excluding] Web of Science Categories=(EVOLUTIONARY BIOLOGY OR COMPUTER SCIENCE THEORY METHODS OR OPERATIONS RESEARCH MANAGEMENT SCIENCE OR SURGERY OR GEOGRAPHY PHYSICAL OR MANAGEMENT OR ZOOLOGY OR ENGINEERING INDUSTRIAL OR AGRICULTURAL ECONOMICS POLICY OR ENVIRONMENTAL SCIENCES OR ENGINEERING CHEMICAL OR MATHEMATICAL COMPUTATIONAL BIOLOGY OR ENGINEERING MECHANICAL OR MATHEMATICS APPLIED OR COMPUTER SCIENCE INFORMATION SYSTEMS OR MINING MINERAL PROCESSING OR TRANSPORTATION OR BIOLOGY OR INFORMATION SCIENCE LIBRARY SCIENCE OR FORESTRY OR ROBOTICS OR AGRICULTURE DAIRY ANIMAL SCIENCE OR ENERGY FUELS OR PLANT SCIENCES OR BIOCHEMISTRY MOLECULAR BIOLOGY OR ENGINEERING MANUFACTURING OR SOIL SCIENCE OR BUSINESS OR THERMODYNAMICS OR BUSINESS FINANCE OR CHEMISTRY	115

	ANALYTICAL OR EDUCATION SCIENTIFIC DISCIPLINES OR COMPUTER SCIENCE SOFTWARE ENGINEERING OR FISHERIES OR ENGINEERING OCEAN OR AGRONOMY OR GEOGRAPHY OR ENTOMOLOGY OR ECOLOGY OR GEOLOGY OR ERGONOMICS OR METEOROLOGY ATMOSPHERIC SCIENCES OR INTERNATIONAL RELATIONS OR GEOCHEMISTRY GEOPHYSICS OR COMPUTER SCIENCE ARTIFICIAL INTELLIGENCE OR LAW OR IMAGING SCIENCE PHOTOGRAPHIC TECHNOLOGY OR LIMNOLOGY OR ENVIRONMENTAL STUDIES OR MATERIALS SCIENCE CHARACTERIZATION TESTING OR MATERIALS SCIENCE MULTIDISCIPLINARY OR ENGINEERING CIVIL OR TELECOMMUNICATIONS OR METALLURGY METALLURGICAL ENGINEERING OR ENGINEERING ELECTRICAL ELECTRONIC OR VETERINARY SCIENCES OR MINERALOGY OR ENGINEERING PETROLEUM OR AGRICULTURAL ENGINEERING OR GEOSCIENCES MULTIDISCIPLINARY OR AGRICULTURE MULTIDISCIPLINARY OR SOCIAL ISSUES OR TRANSPORTATION SCIENCE TECHNOLOGY OR COMPUTER SCIENCE CYBERNETICS OR WATER RESOURCES OR ENGINEERING ENVIRONMENTAL OR URBAN STUDIES OR ENGINEERING MULTIDISCIPLINARY OR AUTOMATION CONTROL SYSTEMS) AND [excluding] Web of Science Categories=(PLANNING DEVELOPMENT) AND [excluding] Subject Areas=(BUSINESS ECONOMICS OR COMPUTER SCIENCE)	

EMBASE (30 July 2011, via Ovid)

Search number	Search	No. of results
1	cost.mp.	420222
2	"value of information".mp.	566
3	"value of of information".mp.	1195
4	"value of of of information".mp.	1543
5	evpi*.mp.	43
6	2 or 3 or 4 or 5	1554
7	1 and 6	345
8	exp "cost benefit analysis"/	55210
9	exp "cost effectiveness analysis"/	73437

10	exp "cost utility analysis"/	3537
11	exp decision making/	106853
12	exp medical decision making/	57338
13	exp decision support system/	8590
14	exp decision theory/	1345
15	exp "decision tree"/	3793
16	exp statistical model/	71792
17	exp health care organization/	866316
18	exp "health care cost"/	162180
19	exp health care planning/	65978
20	exp health care policy/	114734
21	exp health economics/	498628
22	exp probability/	45938
23	exp uncertainty/	3974
24	exp health care delivery/	1406295
25	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	2533843
26	"perfect information".mp.	143
27	(value adj4 information).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2980
28	26 or 27	3026
29	1 and 25 and 28	389
30	limit 29 to yr="1990 - 2010"	353

The Cochrane Library (2 August 2011, 1990-2010)

Search	Search	No. of

number		results
#1	"value of information" or "perfect information" or (evpi*)	106
#2	MeSH descriptor Cost-Benefit Analysis explode all trees	1158
#3	MeSH descriptor Decision Making explode all trees	1932
#4	MeSH descriptor Decision Support Techniques explode all trees	2645
#5	MeSH descriptor Decision Theory explode all trees	727
#6	MeSH descriptor Models, Economic explode all trees	1269
#7	MeSH descriptor Models, Statistical explode all trees	10014
#8	MeSH descriptor Health Care Rationing explode all trees	77
#9	MeSH descriptor Health Care Costs explode all trees	5149
#10	MeSH descriptor Health Policy explode all trees	381
#11	MeSH descriptor Economics, Medical explode all trees	91
#12	MeSH descriptor Markov Chains explode all trees	1267
#13	MeSH descriptor Delivery of Health Care explode all trees	28534
#14	(#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)	46484
#15	value near/4 information	318
#16	perfect information	277
#17	(#15 OR #16)	542
#18	cost	35787
#19	(#14 AND #17 AND #18)	155
#20	(#1 OR #19), from 1990 to 2010	197

CINAHL (4 August 2011, via EBSCOHost)

Search number	Search	No. of results

S1	"Value of information"	127
S2	"Value of * information"	230
S3	"value of * * information"	288
S4	EVPI*	12
S5	S1 or S2 or S3 or S4	288
S6	cost	52045
S7	S5 and S6	80
S8	(MH "Costs and Cost Analysis+") OR (MH "Cost Benefit Analysis")	43453
S9	(MH "Decision Making+")	40667
S10	(MH "Decision Support Techniques+")	1128
S11	(MH "Models, Statistical")	5859
S12	(MH "Health Resource Allocation")	4808
S13	(MH "Health Care Costs+")	18452
S14	(MH "Health Policy+")	38575
S15	(MH "Health Care Delivery+")	129986
S16	(S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15)	217343
S17	"perfect information"	29
S18	value of information	577
S19	S17 or S18	580
S20	S6 and S16 and S19	82
S21	S7 or S20 (Limiters- Published Date from: 19900101-20101231)	89

Full-text searches

AdisOnline (5 August 2011)

Search	No. of results
evpi	21
"expected value of perfect information"	200
Total after deduping	200

HighWire Press (11 August 2011)

Search	No. of results
evpi (all words anywhere in article) In HighWire-hosted journals + Medline From Jan 1990 to Dec 2010	106
“expected value of perfect information” (exact phrase anywhere in article) In HighWire-hosted journals + Medline From Jan 1990 to Dec 2010	139
Total after deduping	156

Cambridge Journals Online (11 August 2011)

Search	No. of results
• Perform new search: evpi • Anywhere: evpi • Exclude book reviews from results: Yes • Restrict search by date range: 01-Jan-1990 to 31-Dec-2010 • Journal: All	11
• Perform new search: "expected value of perfect information" • Exclude book reviews from results: Yes • Restrict search by date range: 01-Jan-1990 to 31-Dec-2010 • Journal: All • Anywhere: "expected value of perfect information"	15

Total after deduping	18

IngentaConnect (11 August 2011)

Search	No. of results
(All Fields including Full Text contains '"expected value of perfect information"')	66
(All Fields including Full Text contains 'evpi')	44
Total after deduping	70

ScienceDirect (11 August 2011)

Search	No. of results
pub-date > 1989 and pub-date < 2011 and ALL(**"expected value of perfect information"**) or ALL(**evpi**)[Journals(Immunology and Microbiology,Medicine and Dentistry,Neuroscience,Nursing and Health Professions,Pharmacology, Toxicology and Pharmaceutical Science)]	59

Scholar (13 August 2011)

Search	No. of results
Cost AND (EVPI OR "expected value of perfect information") 1990–2010	718
Following first screening	179
Total after deduping	175

Health Technology Assessment (30 September 2011)

Search	No. of results

“expected value of perfect information” OR evpi	76
Total after deduping and preliminary screening	14

Appendix 2. Articles included in the review.

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[3] Black C, Clar C, Henderson R, Maceachern C, McNamee P, Quayyum Z, Royle P and Thomas S (2009) 'The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation' Health Technology Assessment 13(52) 1-148

[4] Bojke L, Claxton K, Sculpher M J and Palmer S (2008) 'Identifying research priorities: the value of information associated with repeat screening for age-related macular degeneration' Med Decis Making 28(1) 33-43

[5] Bravo Vergel Y, Hawkins N S, Claxton K, Asseburg C, Palmer S, Woolacott N, Bruce I N and Sculpher M J (2007) 'The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis' Rheumatology 46(11) 1729-1735

[6] Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, Jayne D, Drummond M and Woolacott N (2008) 'Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation' Health Technology Assessment 12(8) 1-193

[7] Carlson J J, Garrison L P, Ramsey S D and Veenstra D L (2009) 'The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer' Value in Health 12(1) 20-27

[8] Carlton J, Karnon J, Czoski-Murray C, Smith K J and Marr J (2008) 'The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4-5 years: a systematic review and economic evaluation' Health Technology Assessment 12(25)

[9] Castelnuovo E, Cross P, Mt-Isa S, Spencer A, Underwood M and on behalf of the TOIB study team (2008) 'Cost-effectiveness of advising the use of topical or oral ibuprofen for knee pain; the TOIB study [ISRCTN: 79353052]' Rheumatology 47(7) 1077-1081

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[11] Claxton K, Neumann P J, Araki S and Weinstein M C (2001) 'Bayesian value-of-information analysis. An application to a policy model of Alzheimer's disease' International Journal of Technology Assessment in Health Care 17(1) 38-55

[12] Clegg A, Loveman E, Gospodarevskaya E, Harris P, Bird A, Bryant J, Scott D A, Davidson P, Little P and Coppin R (2010) 'The safety and effectiveness of different methods of ear wax removal: A systematic review and economic evaluation' Health Technology Assessment 14(28)

[13] Colbourn T E, Asseburg C, Bojke L, Philips Z, Welton N J, Claxton K, Ades A E and Gilbert R E (2007) 'Preventive strategies for group B streptococcal and other bacterial infections in early infancy: cost effectiveness and value of information analyses' BMJ 335(7621) 655

[14] Coyle D, Coyle K, Vale L, de V R, Imamura M, Glazener C and Zhu S (2008) 'Minimally invasive arthroplasty in the management of hip arthritic disease: systematic review and economic evaluation' Ottawa: Canadian Agency for Drugs and Technologies in Health

[15] da Silveira E B and Artifon E L (2008) 'Cost-effectiveness of palliation of unresectable esophageal cancer' Digestive Diseases and Sciences 53(12) 3103-3111

[16] Dong H, Coyle D and Buxton M (2007) 'Value of information analysis for a new technology: Computer-assisted total knee replacement' International Journal of Technology Assessment in Health Care. 23(3) 337-342

[17] Eddama O, Petrou S, Regier D, Norrie J, MacLennan G, Mackenzie F and Norman J E (2010) 'Study of progesterone for the prevention of preterm birth in twins (STOPPIT): findings from a trial-based cost-effectiveness analysis' International Journal of Technology Assessment in Health Care 26(2) 141-148

[18] Ehlers L, Overvad K, Sorensen J, Christensen S, Bech M and Kjolby M (2009) 'Analysis of cost effectiveness of screening Danish men aged 65 for abdominal aortic aneurysm' BMJ (Clinical Research Ed.) 338 b2243

[19] Fenwick E, Palmer S, Claxton K, Sculpher M, Abrams K and Sutton A (2006) 'An iterative bayesian approach to health technology assessment: application to a policy of preoperative optimization for patients undergoing major elective surgery' Med. Decis. Making 26(5) 480-496

[20] Fleurence R L (2007) 'Setting priorities for research: a practical application of 'payback' and expected value of information' Health Economics 16(12) 1345-1357

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[22] Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A and Taylor R S (2007) 'The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model' Health Technology Assessment 11(47)

[23] Galani C, Al M, Schneider H and Rutten F F H (2005) 'Uncertainty in Decision-Making: Value of Additional Information in the Cost-Effectiveness of Lifestyle Intervention in Overweight and Obese People' Value in Health 11(3) 424-434

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[25] Ginnelly L, Claxton K, Sculpher M J and Golder S (2005) 'Using value of information analysis to inform publicly funded research priorities' Applied Health Economics and Health Policy 4(1) 37-46

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[27] Gold H T, Hall M J, Blinder V and Schackman B R (2009) 'Cost effectiveness of pharmacogenetic testing for UGT1A1 before irinotecan administration for metastatic colorectal cancer' Cancer 115(17) 3858

[28] Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, Macran S, Kilonzo M, Vale L, Francis J et al (2008) 'The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial' Health Technology Assessment 12(31) 1-204

[29] Griebsch I, Knowles R L, Brown J, Bull C, Wren C and Dezateux C A (2007) 'Comparing the clinical and economic effects of clinical examination, pulse oximetry, and echocardiography in newborn screening for congenital heart defects: a probabilistic cost-effectiveness model and value of information analysis' International Journal of Technology Assessment in Health Care 23(2) 192-204

[30] Groot Koerkamp B, Spronk S, Stijnen T and Hunink M G (2010) 'Value of information analyses of economic randomized controlled trials: the treatment of intermittent claudication' Value in Health 13(2) 242-250

[31] Groot Koerkamp B, Nikken J J, Oei E H, Stijnen T, Ginai A Z and Hunink M G M (2008) 'Value of information analysis used to determine the necessity of additional research: MR imaging in acute knee trauma as an example' Radiology 246(2) 420-425

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Appendix 3. Data extracted from included articles (references appear in Appendix 2).

First author	Publication year	Funder	Location	Individual EVPI	Population EVPI (£)	WTP threshold	Outcome measure	Currency	Timeframe
Armstrong [1]	2009	Government	UK		5300000	20000	QALY	GBP	not stated
Bansback [2]	2004	Academic	UK		246000	30000	QALY	GBP	1 year
Black [3]	2009	Government	UK		600000000	30000	QALY	GBP	10 years
Bojke [4]	2008	Government	UK		6900000	30000	QALY	GBP	10 years
Bravo [5]	2007	Government	UK		23046814	not stated	QALY	GBP	10 years
Burch [6]	2008	Government	UK		16000000	30000	QALY	GBP	8 years
Carlson [7]	2009	Industry-related	US	381	31400000	100000	QALY	USD	5 years
Carlton [8]	2008	Government	UK		45000000	17000	QALY	GBP	10 years
Castelnuovo [9]	2006	Government	UK		16900000	30000	QALY	GBP	15 years
Castelnuovo [10]	2008	Industry-related	UK		170000000	30000	QALY	GBP	10 years
Claxton [11]	2001	Charity	US		339000000	50000	QALY	USD	averaged over 2 to 8

									years
Clegg [12]	2010	Government	UK		14000000	23000	QALY	GBP	10 years
Colbourn [13]	2007	Government	UK		67300000	25000	QALY	GBP	10 years
Coyle [14]	2008	Government	Canada	3247	480000000	50000	QALY	Can$	10 years
Da Silveira [15]	2008	Academic	US		24000000	5000	per improvement in swallowing graded by the dysphagia score	USD	20 years
Dong [16]	2007	Industry-related	UK	21.4	8300000	30000	QALY	GBP	10 years
Eddama [17]	2010	Government	UK	almost £100.00 per woman	1033400	30000	per prevention of preterm birth	GBP	1 year
Ehlers [18]	2009	Government	Denmark		1000000	30000	QALY	GBP	20 years
Fenwick [19]	2006	Industry-related	UK	350	48000000	20000	life year	GBP	15 years
Fleurence [20]	2007	Government	UK		608000000	30000	QALY	GBP	5 years
Forbes [21]	2002	Government	UK	800	10700000	30000	life years gained	GBP	5 years

Fox [22]	2007	Government	UK	157	6200000	30000	QALY	GBP	7 years
Galani [23]	2008	Government	Switzerland	198	6785783	5000	QALY	CHF	10 years
Genders [24]	2009	Government	Netherlands	46 per woman	380000000	80000	QALY	euros	5 years
Ginnelly [25]	2005	Government	UK		2240000	30000	QALY	GBP	10 years
Girling [26]	2007	Industry-related	UK	395	28000000	30000	QALY	GBP	5 years
Gold [27]	2009	Charity	US		13800000	100000	QALY	USD	5 years
Grant [28]	2008	Government	UK		300000000	30000	QALY	GBP	annual?
Griebsch [29]	2007	Government	UK		744000	50000	timely diagnosis of "lifethreatening" CHD	GBP	5 years
Groot Koerkamp [30]	2010	Government	Netherlands	249	11000000	80000	QALY	euros	5 years
Groot Koerkamp [31]	2008	Government	Netherlands	2.1	365000	80000	QALY	euros	10 years
Grutters [32]	2008	Government	Netherlands	87	100000000	40000	QALY	euros	10 years
Grutters [33]	2010	Industry-related	Netherla	7784	22000000	80000	QALY	euros	10 years

			nds						
Hassan [34]	2009	Industry-related	US	520	56777030	100000	life years gained	USD	10 years
Hassan [35]	2010	Academic	US	16647	1099357520	150000	life years gained	USD	5 years
Hassan [36]	2009	Industry-related	US	216	15291170112	100000	life years gained	USD	5 years
Henriksson [37]	2006	Government	sweden	0.33	115000	50000	QALY	euros	10 years
Hewitt [38]	2009	Government	UK		40075803	30000	QALY	GBP	10 years
Hoomans [39]	2009	Academic	UK		13400000	30000	QALY	GBP	1.5 years
Iglesias [40]	2006	Academic	UK		126700	500	QALY	GBP	10 years
Jansen [41]	2010	Industry-related	UK		80000	20000	QALY	GBP	30 years
Karnon [42]	2002	Government	UK	239.08	7045615	5000	QALY	GBP	5 years
Kim [43]	2010	Academic	South Korea		120000000000	8000000	QALY	KRW	5 years
Knight [44]	2004	Government	UK	53	159000	30000	QALY	GBP	1 year
Knowles [45]	2005	Government	UK		750000	5000	timely diagnosis	GBP	5 years
Kulkarni [46]	2009	Academic	Canada	28220	275000000	50000	QALY	Can$	1 year
Martikainen [47]	2005	Industry-related	Finland		4100000	32471	QALY	euros	10 years

McKenna [48]	2009	Government	UK	440.16	48741220	30000	QALY	GBP	10 years
McKenna [49]	2010	Government	UK	2694	696178334	30000	QALY	GBP	10 years
Meenan [50]	2007	Government	US	<100	20000000	50000	QALY	USD	1 year
Meltzer [51]	2009	Industry-related	US		308000000000	50000	QALY	USD	20 years
Miners [52]	2009	Industry-related	UK	44000	20000000	30000	QALY	GBP	10 years
Oostenbrink [53]	2008	Industry-related	Netherlands	1070	96000000	20000	QALY	euros	1 year?
Pandor [54]	2004	Government	UK		3656	2000	life year gained	GBP	5 years
Payne [55]	2000	Government	UK		200000	20000	life years saved	GBP	5 years
Petrou [56]	2010	Industry-related	UK	65.73	9100000	20000	QALY	GBP	10 years
Philips [57]	2006	Academic	UK	43	20032000	30000	QALY	GBP	10 years
Pohar [58]	2009	Government	Canada	19157	19000000	50000	QALY	Can$	1 year
Quinn [59]	2007	Industry-related	Canada	1821	76482000	50000	QALY	USD	1 year
Ramsey [60]	2008	Government	US		46000000	50000	QALY	USD	10 years
Rao [61]	2009	Industry-related	UK		35554.50	50000	QALY	USD	4 years
Rodgers [62]	2008	Government	UK	635.01	5465967	30000	QALY	GBP	5 years

Rogowski [63]	2009	Government	UK		10762438	30000	QALY	GBP	10 years
Rojnik [64]	2008	Industry-related	Slovenia	23	115000000	20000	QALY	euros	10 years
Shepherd [65]	2010	Government	UK		12500000	20000	QALY	GBP	10 years
Singh [66]	2008	Academic	Canada	32.59	16300000	20000	per inappropriate ACS discharge prevented	Can$	1 year
Smith [67]	2007	Government	US	532	1666224	100000	QALY	USD	10 years
Smits [68]	2010	Government	US	1759	7000000000	75000	QALY	USD	
Somerville [69]	2008	Government	UK	148	6553619	30000	QALY	GBP	10 years
Speight [70]	2006	Government	UK		277000000	30000	QALY	GBP	10 years
Spronk [71]	2008	Academic	Netherlands	1743	2400000000	75000	QALY	USD	10 years
Spronk [72]	2008	Academic	Netherlands/US	30	39000000	50000	QALY	euros	5 years
Stevenson [73]	2010	Government	UK	53.50	64000000	not explicitly stated in context of EVPI	QALY	GBP	10 years
Tappenden [74]	2004	Government	UK	8855	86208936	30000	QALY	GBP	10 years

Teerawattananon [75]	2007	Government	Thailand		2600000000	650000	QALY	Thai baht	10 years
TEN [76]	2009	Government	Netherlands	32	27000000	40000	QALY	euros	10 years
Tholen [77]	2010	Government	Netherlands	318	1500000000	50000	QALY	euros	5 years
Tran [78]	2010	Government	Canada	172	295000000	50000	QALY	Can$	1 year
Van der Sluis [79]	2010	Academic	Netherlands	282	423000000	80000	QALY	euros	5 years
Van Loon [80]	2009	Academic	Netherlands	810	3245786	75000	QALY	USD	5 years
Wailoo [81]	2008	Government	UK		2000000	30000	QALY	GBP	15 years
Weatherly [82]	2009	Government	UK	183	33000000	20000	QALY	GBP	5 years
Welton [83]	2008	Government	UK		932000000	30000	QALY	GBP	10 years
Wight [84]	2003	Government	UK	125	812500	20000	QALY	GBP	5 years
Wilson [85]	2010	Academic	UK		18800000	20000	QALY	GBP	10 years
Xie [86]	2009	Government	Canada	0	0	30000	QALY	Can$	

Appendix 4. Predicted probability of positive recommendation at different EVPI values for 'full' model, holding all covariates constant at baseline values

Figure 1. Predicted probability of positive recommendation at different EVPI values by country classification

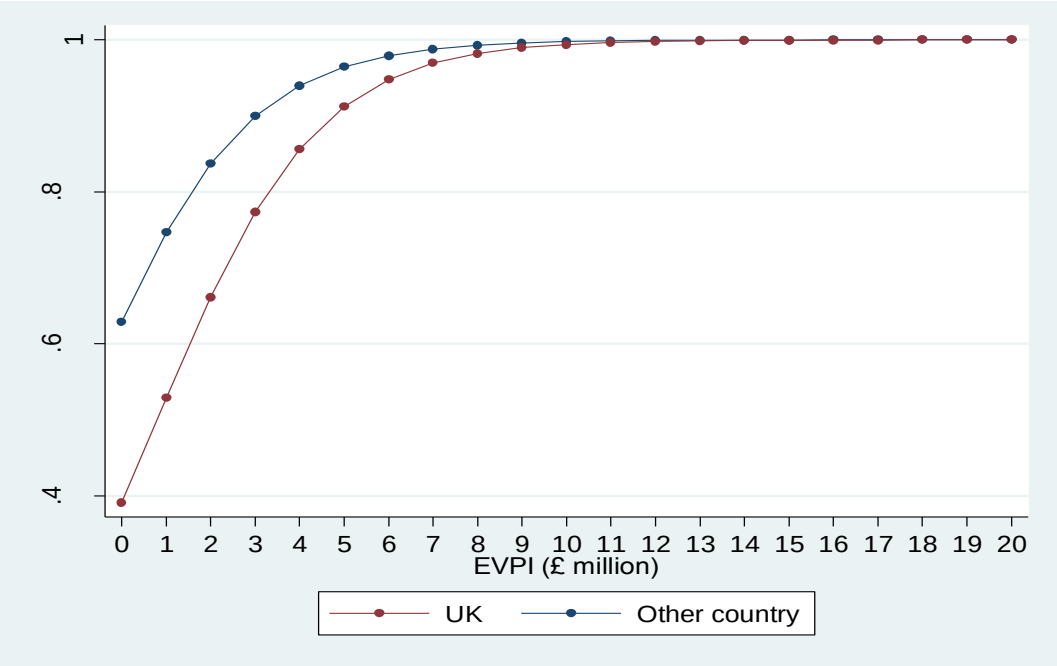

Figure 2. Predicted probability of positive recommendation at different EVPI values by disease classification

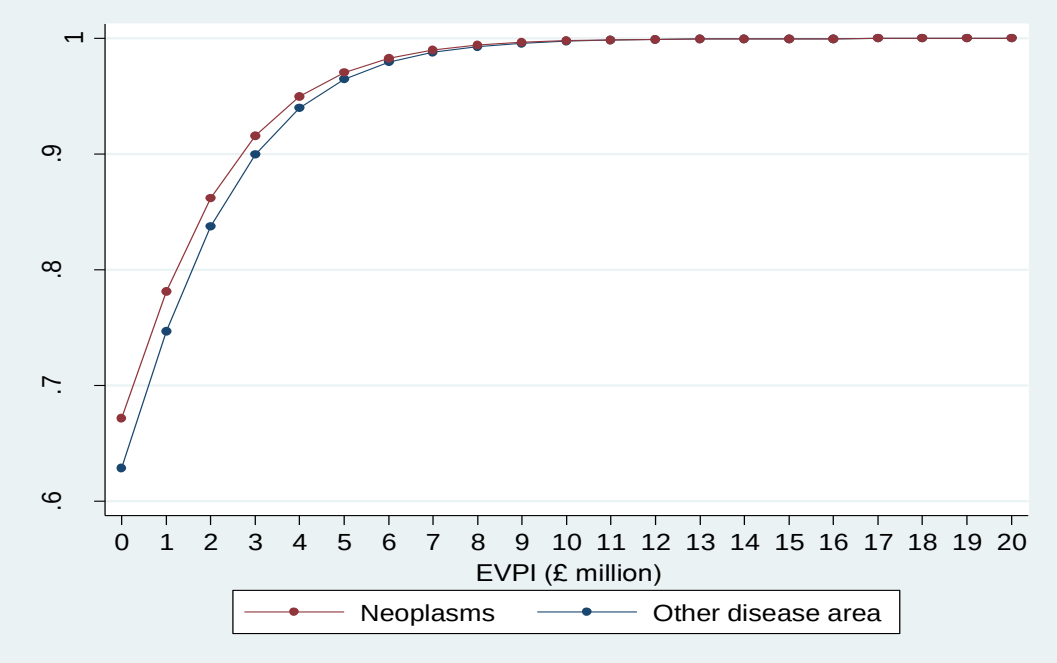

Figure 3. Predicted probability of positive recommendation at different EVPI values by study funder

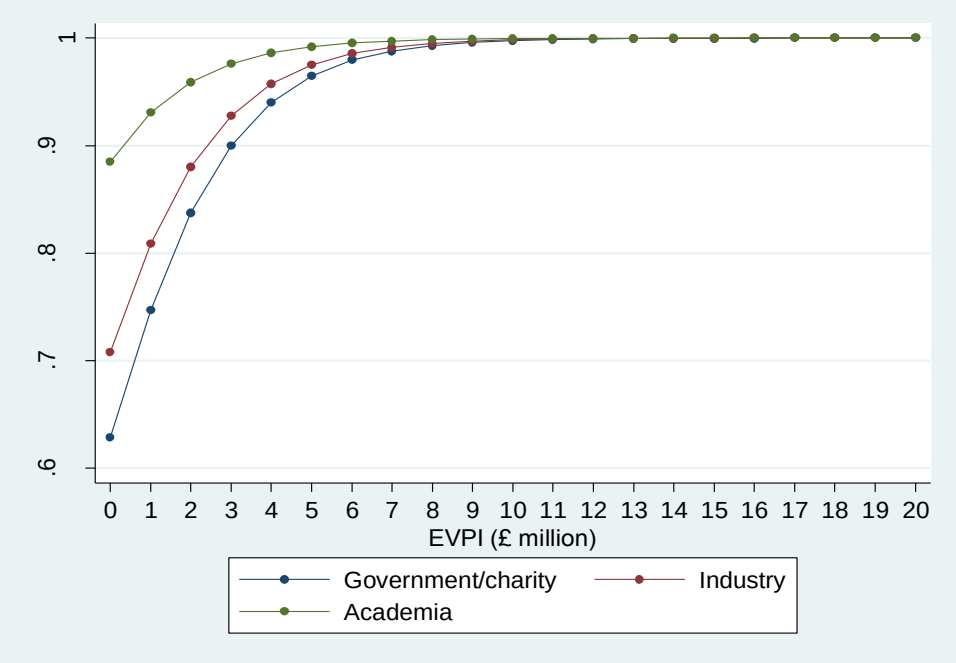

Figure 4. Predicted probability of positive recommendation at different EVPI values by outcome

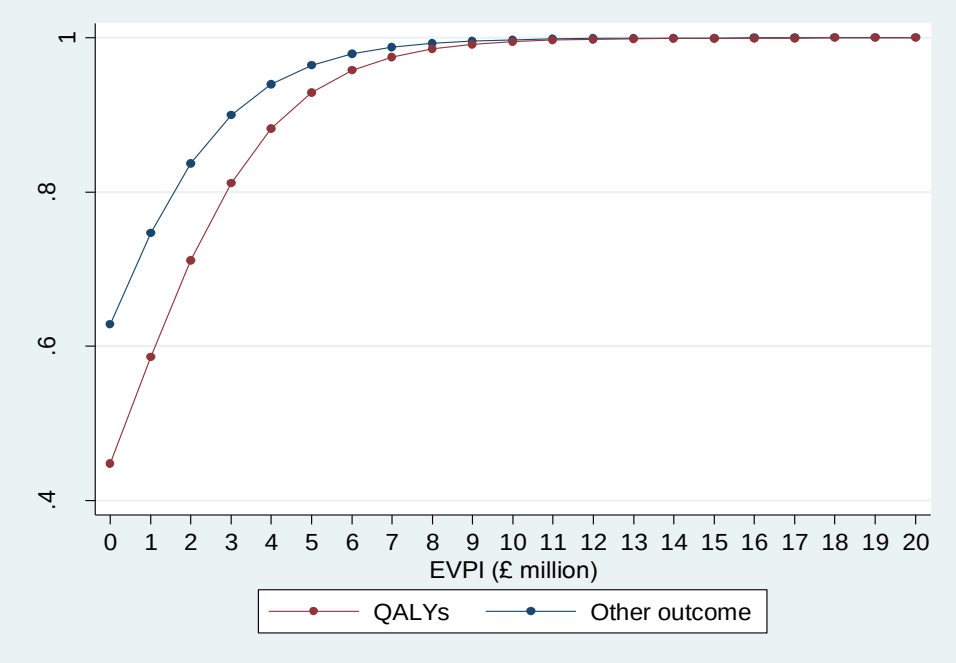

Figure 5. Predicted probability of positive recommendation at different EVPI values by publication year