

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

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

## **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 Vol 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 Vol 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 Vol 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 Vol 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 Vol 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

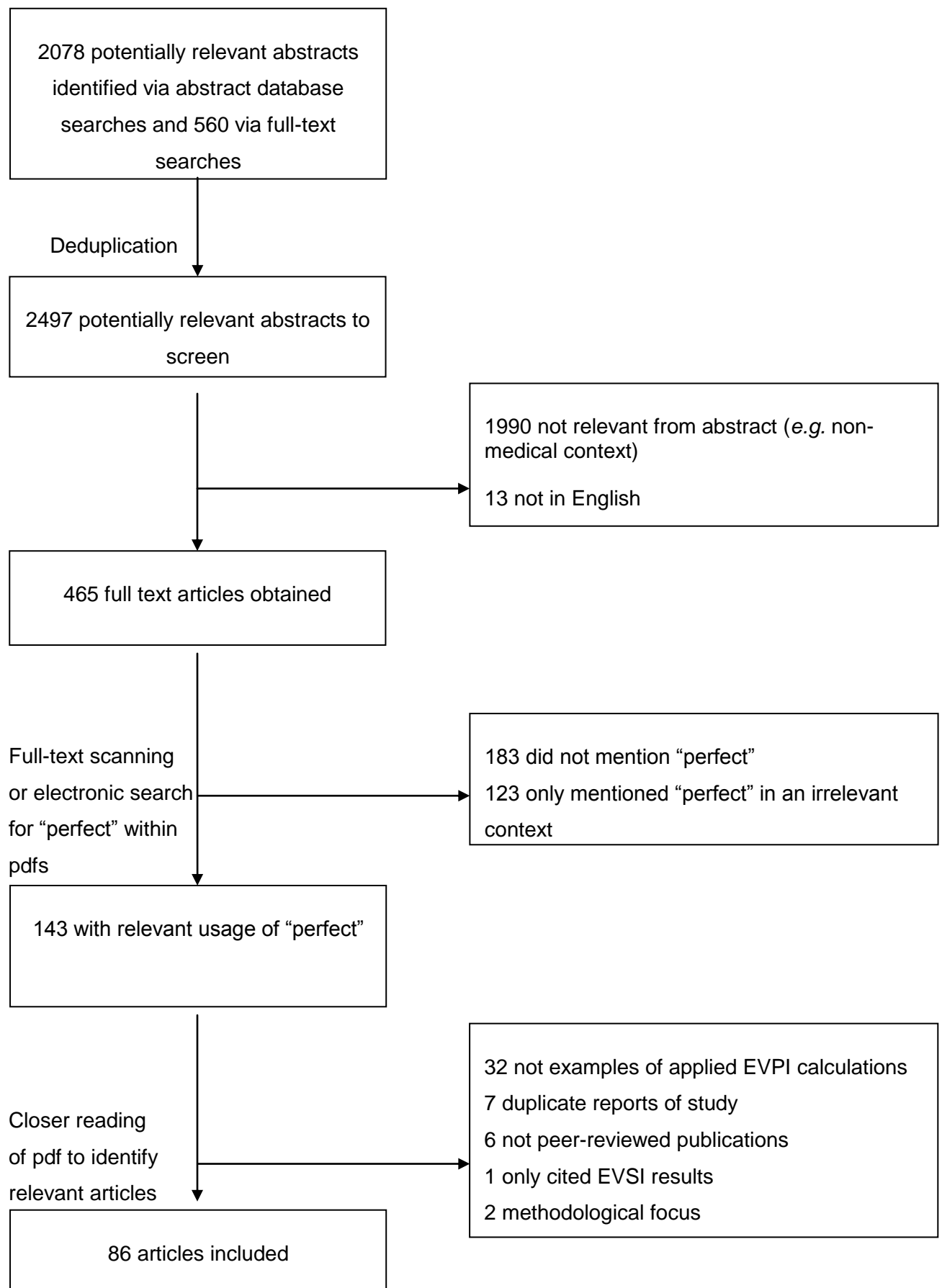
| Characteristic          |                        | Number (%) |
|-------------------------|------------------------|------------|
| <b>Funder</b>           |                        |            |
|                         | Government             | 53 (61.6)  |
|                         | Industry-related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



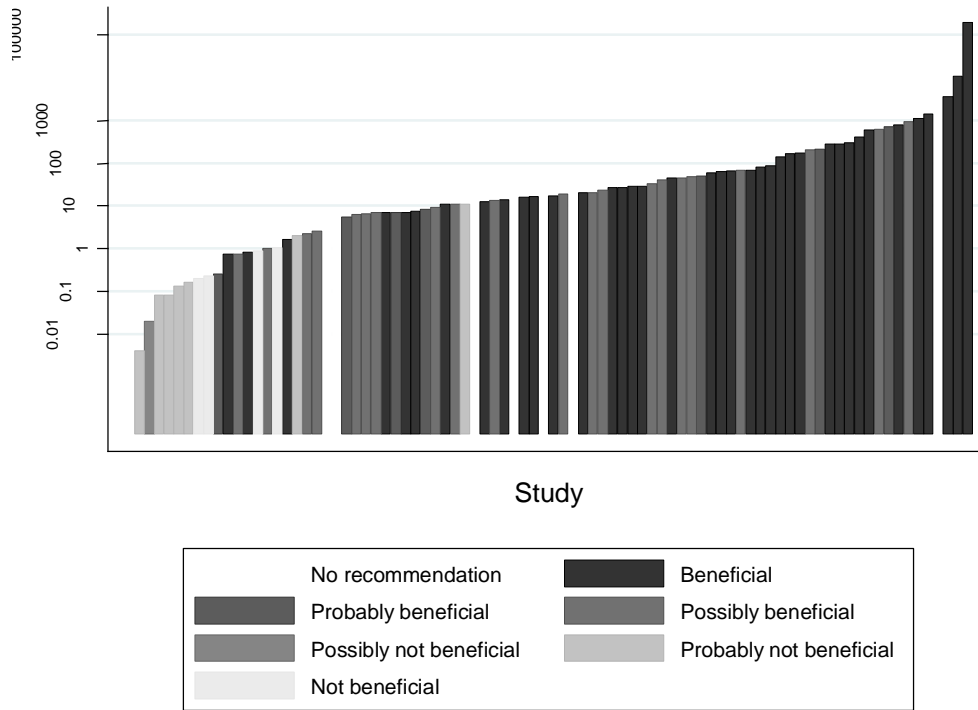
**Table 2. Results of 'EVPI only' and 'full' models**

| Model   | Predictor variables                          | Odds ratio | SE    | P> z  | 95% Confidence interval |        | Likelihood ratio | McFadden's adjusted R <sup>2</sup> | 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) |  |            |       |       |                         |        |                  |                                    |       |                              |                                |

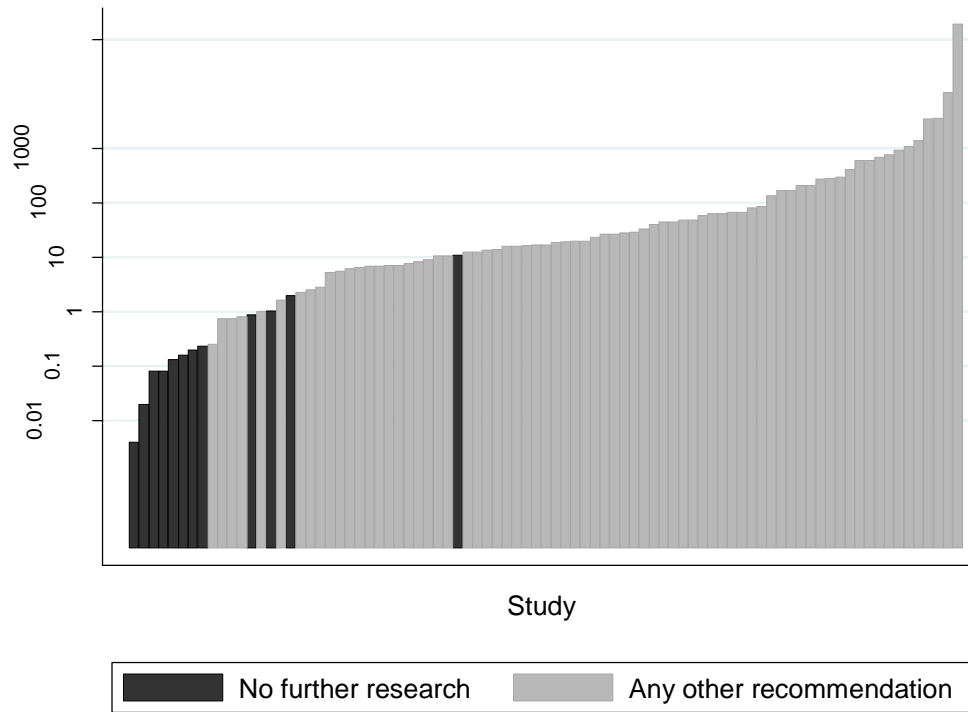
Figure 1. Flowchart



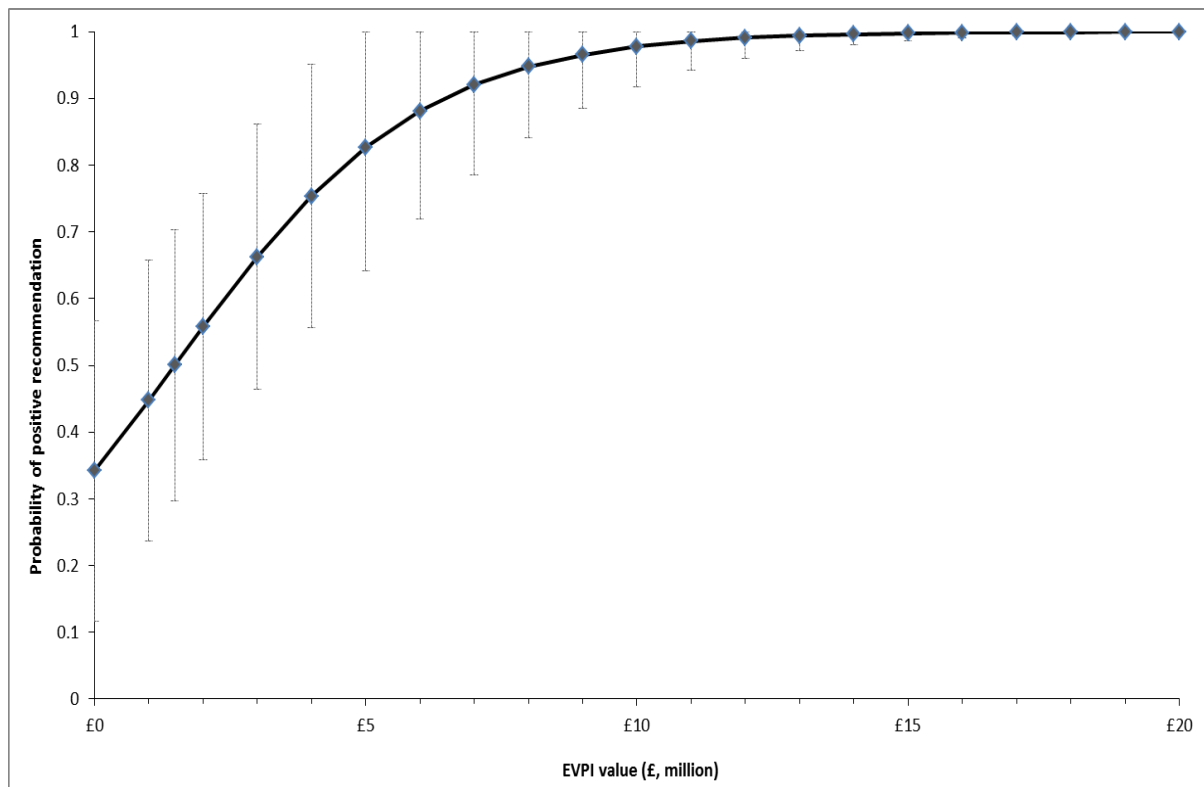
**Figure 2.** Recommendations for further research by EVPI value; values are plotted on a log scale.



**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<br><br>Refined by: [excluding] Web of Science Categories=(<br>EVOLUTIONARY BIOLOGY OR COMPUTER SCIENCE THEORY<br>METHODS OR OPERATIONS RESEARCH MANAGEMENT<br>SCIENCE OR SURGERY OR GEOGRAPHY PHYSICAL OR<br>MANAGEMENT OR ZOOLOGY OR ENGINEERING INDUSTRIAL<br>OR AGRICULTURAL ECONOMICS POLICY OR<br>ENVIRONMENTAL SCIENCES OR ENGINEERING CHEMICAL<br>OR MATHEMATICAL COMPUTATIONAL BIOLOGY OR<br>ENGINEERING MECHANICAL OR MATHEMATICS APPLIED OR<br>COMPUTER SCIENCE INFORMATION SYSTEMS OR MINING<br>MINERAL PROCESSING OR TRANSPORTATION OR BIOLOGY<br>OR INFORMATION SCIENCE LIBRARY SCIENCE OR<br>FORESTRY OR ROBOTICS OR AGRICULTURE DAIRY ANIMAL<br>SCIENCE OR ENERGY FUELS OR PLANT SCIENCES OR<br>BIOCHEMISTRY MOLECULAR BIOLOGY OR ENGINEERING<br>MANUFACTURING OR SOIL SCIENCE OR BUSINESS OR<br>THERMODYNAMICS OR BUSINESS FINANCE OR CHEMISTRY | 115            |

|  |  |  |
|--|--|--|
|  | ANALYTICAL OR EDUCATION SCIENTIFIC DISCIPLINES OR<br>COMPUTER SCIENCE SOFTWARE ENGINEERING OR<br>FISHERIES OR ENGINEERING OCEAN OR AGRONOMY OR<br>GEOGRAPHY OR ENTOMOLOGY OR ECOLOGY OR GEOLOGY<br>OR ERGONOMICS OR METEOROLOGY ATMOSPHERIC<br>SCIENCES OR INTERNATIONAL RELATIONS OR<br>GEOCHEMISTRY GEOPHYSICS OR COMPUTER SCIENCE<br>ARTIFICIAL INTELLIGENCE OR LAW OR IMAGING SCIENCE<br>PHOTOGRAPHIC TECHNOLOGY OR LIMNOLOGY OR<br>ENVIRONMENTAL STUDIES OR MATERIALS SCIENCE<br>CHARACTERIZATION TESTING OR MATERIALS SCIENCE<br>MULTIDISCIPLINARY OR ENGINEERING CIVIL OR<br>TELECOMMUNICATIONS OR METALLURGY METALLURGICAL<br>ENGINEERING OR ENGINEERING ELECTRICAL ELECTRONIC<br>OR VETERINARY SCIENCES OR MINERALOGY OR<br>ENGINEERING PETROLEUM OR AGRICULTURAL<br>ENGINEERING OR GEOSCIENCES MULTIDISCIPLINARY OR<br>AGRICULTURE MULTIDISCIPLINARY OR SOCIAL ISSUES OR<br>TRANSPORTATION SCIENCE TECHNOLOGY OR COMPUTER<br>SCIENCE CYBERNETICS OR WATER RESOURCES OR<br>ENGINEERING ENVIRONMENTAL OR URBAN STUDIES OR<br>ENGINEERING MULTIDISCIPLINARY OR AUTOMATION<br>CONTROL SYSTEMS ) AND [excluding] Web of Science<br>Categories=( PLANNING DEVELOPMENT ) AND [excluding]<br>Subject Areas=( BUSINESS ECONOMICS OR COMPUTER<br>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            |
| <b>Total after deduping</b>             | <b>200</b>     |

### HighWire Press (11 August 2011)

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

### Cambridge Journals Online (11 August 2011)

| Search  | No. of results |
|---|----------------|
| <ul style="list-style-type: none"><li>Perform new search: evpi</li><li>Anywhere: evpi</li><li>Exclude book reviews from results: Yes</li><li>Restrict search by date range: 01-Jan-1990 to 31-Dec-2010</li><li>Journal: All</li></ul>   | 11             |
| <ul style="list-style-type: none"><li>Perform new search: "expected value of perfect information"</li><li>Exclude book reviews from results: Yes</li><li>Restrict search by date range: 01-Jan-1990 to 31-Dec-2010</li><li>Journal: All</li><li>Anywhere: "expected value of perfect information"</li></ul> | 15             |

|                             |    |
|-----------------------------|----|
|                             |    |
| <b>Total after deduping</b> | 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             |
| <b>Total after deduping</b>   | 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            |
| <b>Total after deduping</b>  | 175            |

**Health Technology Assessment** (30 September 2011)

| Search | No. of results |
|--------|----------------|
|--------|----------------|

|   |    |
|---|----|
| "expected value of perfect information" OR evpi       | 76 |
| <b>Total</b> after deduping and preliminary screening | 14 |

## Appendix 2. Articles included in the review.

- [1] Armstrong N, Vale L, Deverill M, Nabi G, McClinton S, N'Dow J and Pickard R (2009) 'Surgical treatments for men with benign prostatic enlargement: cost-effectiveness study' *BMJ* 338 b1288
- [2] Bansback N, Ward S and Karnon J (2004) "Economic evaluation of gemcitabine in the treatment of pancreatic cancer in the UK": How important is quality of life?' *The European Journal of Health Economics* 5(2) 188-189
- [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)
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- [10] Castelnovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A and Stein K (2006) 'The cost-effectiveness of testing for hepatitis C in former injecting drug users' *Health Technology Assessment* 10(32)
- [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
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- [21] Forbes C, Wilby J, Richardson G, Sculpher M, Mather L and Riemsma R (2002) 'A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer' *Health Technology Assessment* 6(23) 1-119
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- [26] Girling A J, Freeman G, Gordon J P, Poole-Wilson P, Scott D A and Lilford R J (2007) 'Modeling payback from research into the efficacy of left-ventricular assist devices as destination therapy' *International Journal of Technology Assessment in Health Care* 23(2) 269-277
- [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
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- [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

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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"<br>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 | Netherlands | 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          |        | 134000000    | 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  | 2750000000   | 50000   | QALY              | Can\$ | 1 year    |
| Martikainen [47] | 2005 | Industry-related | Finland     |        | 4100000      | 32471   | QALY              | euros | 10 years  |

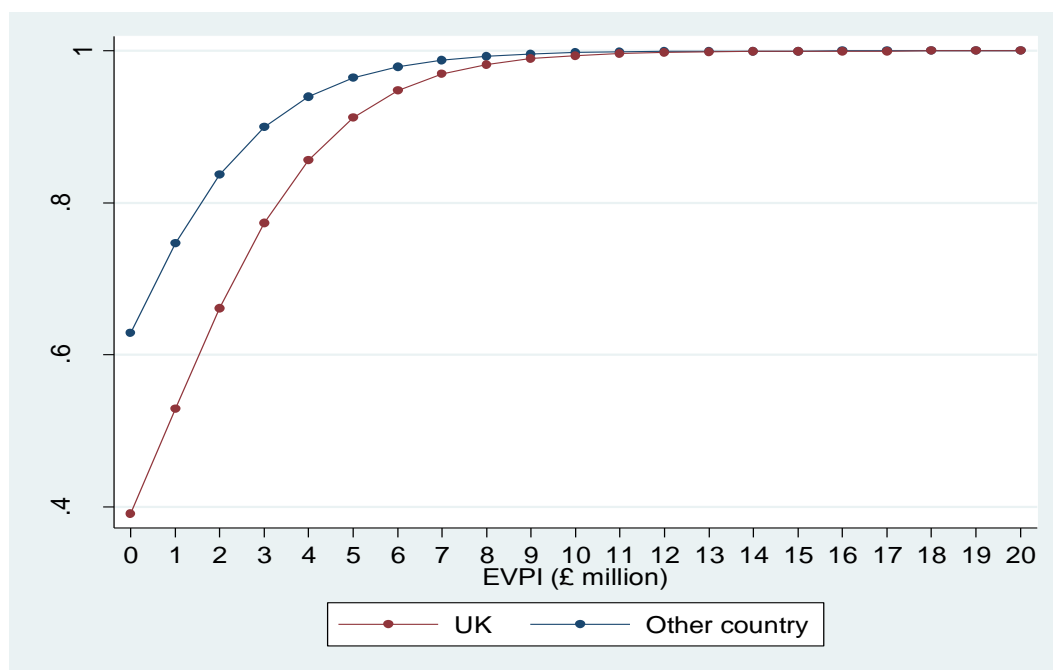
|                  |      |                  |             |        |              |       |                  |       |          |
|------------------|------|------------------|-------------|--------|--------------|-------|------------------|-------|----------|
| McKenna [48]     | 2009 | Government       | 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 inappropriat<br>e ACS<br>discharge<br>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         | Netherla<br>nds    | 1743  | 2400000000 | 75000  | QALY  | USD   | 10 years |
| Spronk [72]     | 2008 | Academic         | Netherla<br>nds/US | 30    | 39000000   | 50000  | QALY  | euros | 5 years  |
| Stevenson [73]  | 2010 | Government       | UK                 | 53.50 | 64000000   | not<br>explicitly<br>stated in<br>context of<br>EVPI | QALY  | GBP   | 10 years |
| Tappenden [74]  | 2004 | Government       | UK                 | 8855  | 86208936   | 30000  | QALY  | GBP   | 10 years |

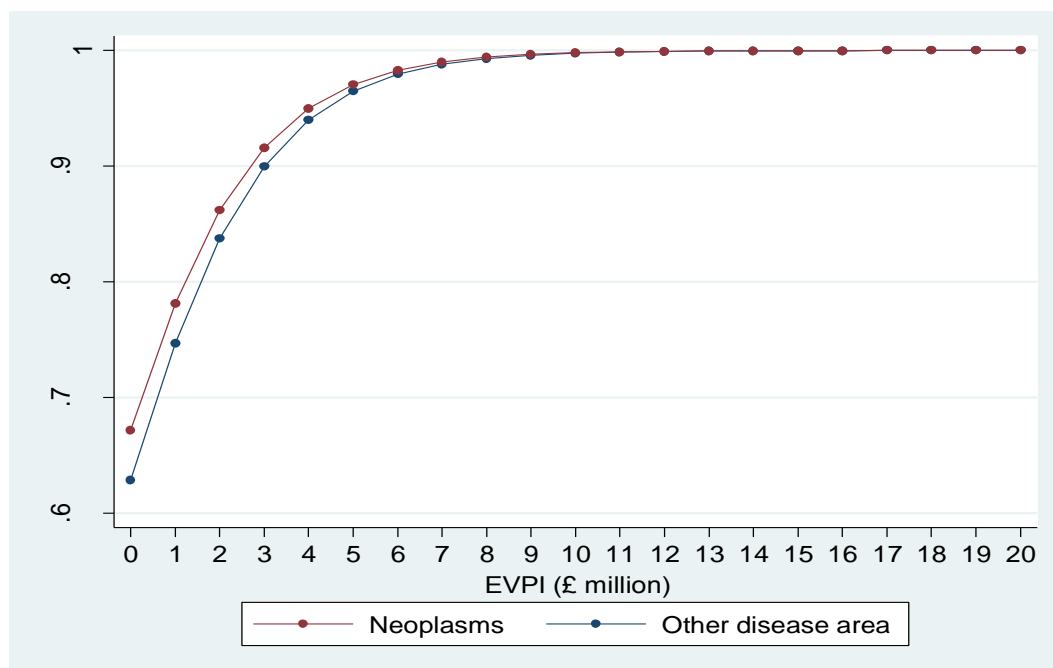
|                      |      |            |             |     |              |        |      |           |          |
|----------------------|------|------------|-------------|-----|--------------|--------|------|-----------|----------|
| Teerawattananon [75] | 2007 | Government | Thailand    |     | 260000000000 | 650000 | QALY | Thai baht | 10 years |
| TEN [76]             | 2009 | Government | Netherlands | 32  | 270000000    | 40000  | QALY | euros     | 10 years |
| Tholen [77]          | 2010 | Government | Netherlands | 318 | 15000000000  | 50000  | QALY | euros     | 5 years  |
| Tran [78]            | 2010 | Government | Canada      | 172 | 2950000000   | 50000  | QALY | Can\$     | 1 year   |
| Van der Sluis [79]   | 2010 | Academic   | Netherlands | 282 | 4230000000   | 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 | 330000000    | 20000  | QALY | GBP       | 5 years  |
| Welton [83]          | 2008 | Government | UK          |     | 9320000000   | 30000  | QALY | GBP       | 10 years |
| Wight [84]           | 2003 | Government | UK          | 125 | 812500       | 20000  | QALY | GBP       | 5 years  |
| Wilson [85]          | 2010 | Academic   | UK          |     | 188000000    | 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

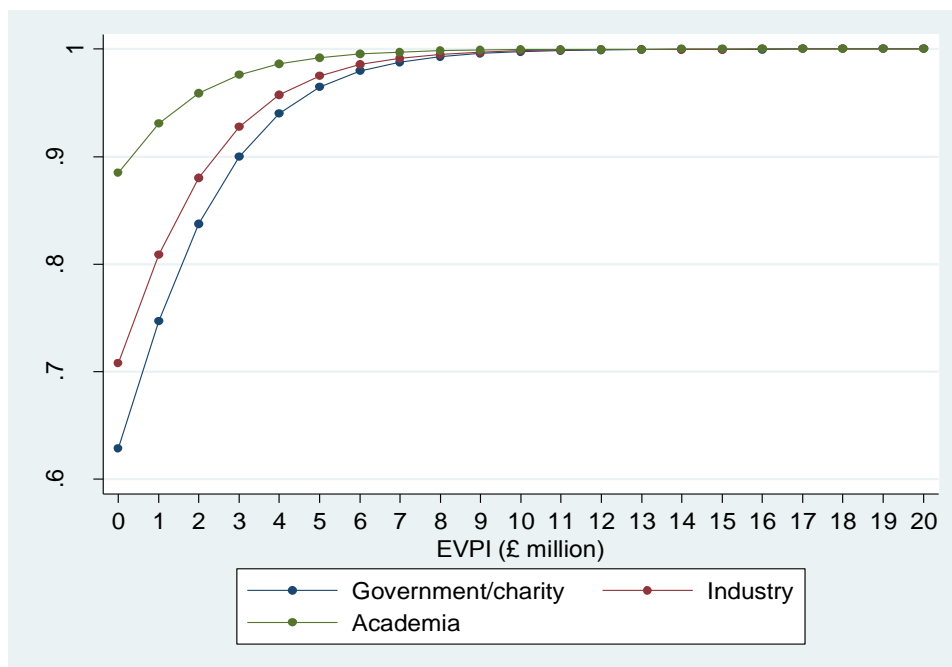
Figure 1. Predicted probability of positive recommendation at different EVPI values by country classification



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

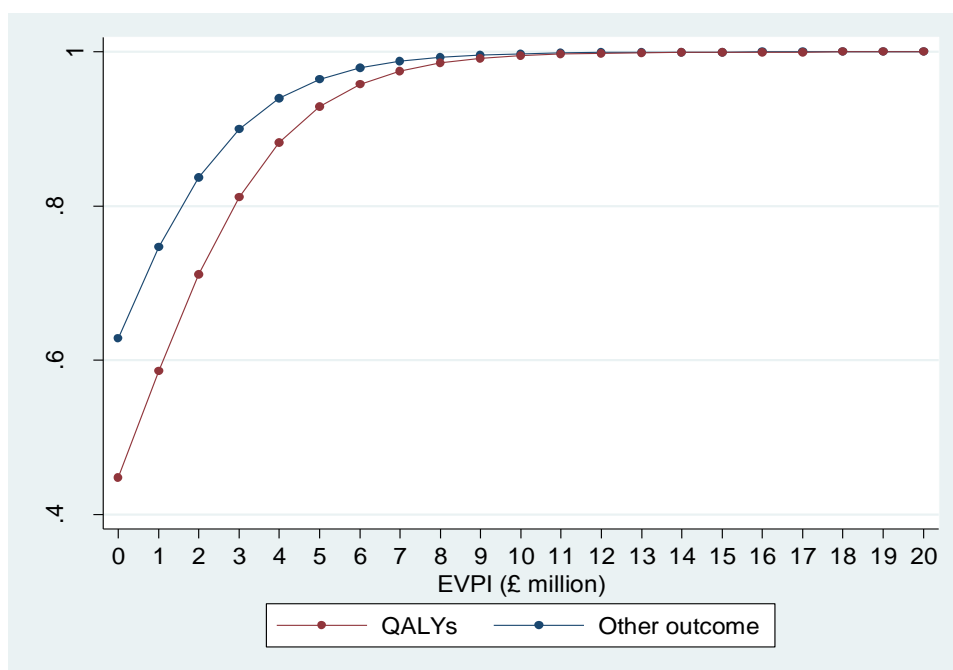


**Figure 3. Predicted probability of positive recommendation at different EVPI values by study funder**





**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**