**ABSTRACT**

**Objectives:** Productivity losses usually have a considerable impact on cost-effectiveness estimates while their estimated values are often relatively uncertain. Therefore, parameters related to these indirect costs play a role in setting priorities for future research from a societal perspective. Until now, however, value of information analyses have usually applied a health care perspective for economic evaluations. Hence, the effect of productivity losses has rarely been investigated in such analyses. The aim of the current study therefore was to investigate the effects of including or excluding productivity costs in value of information analyses. **Methods:** Expected value of information analysis (EVPI) was performed in cost-effectiveness evaluation of prevention from both societal and health care perspectives, to give us the opportunity to compare different perspectives. Priorities for future research were determined by partial EVPI. The program to prevent major depression in patients with subthreshold depression was opportunistic screening followed by minimal contact psychotherapy. **Results:** The EVPI indicated that regardless of perspective, further research is potentially worthwhile. Partial EVPI results underlined the importance of productivity losses when a societal perspective was considered. Furthermore, priority setting for future research differed according to perspective. **Conclusions:** The results illustrated that advise for future research will differ for a health care versus a societal perspective and hence the value of information analysis should be adjusted to the perspective that is relevant for the decision makers involved. The outcomes underlined the need for carefully choosing the suitable perspective for the decision problem at hand. **Keywords:** cost-effectiveness, perspective, productivity costs, uncertainty, value of information analysis.

**Introduction**

Estimates of cost-effectiveness are surrounded by uncertainty. Reduction of uncertainty is usually costly. A value of information (VOI) analysis estimates the monetary value of investments that may be required to eliminate all or part of uncertainty in the evaluations. Such estimation can support the decision maker in deciding whether further research is warranted [1]. When further research turns out to be worthwhile, more detailed VOI analysis can identify the uncertainties that should then become research priorities. VOI for parameters estimates the expected VOIs on groups of parameters and assists the decision maker to decide on those uncertainties. The concept of VOI analysis [1] was applied in many sectors [2] before it was introduced in health technology assessment by Claxton [3]. Recently, the number of applications in health care has steadily grown. A range of studies was published after 2004 [4–13].

While the societal perspective is recommended for economic evaluations in many countries [14], the majority of the previous studies have applied a health care perspective in analyzing the VOI. Studies performed in the United Kingdom were just following national directives in adopting a health care perspective according to The Guidelines Manual [15]. Also, among the non-UK studies, however, only a few have taken into account other than direct health care costs. Some included direct non–health care or some national directives in adopting a health care perspective according to The Guidelines Manual [15]. Also, among the non-UK studies, however, only a few have taken into account other than direct health care costs. Some included direct non–health care or some part of indirect health care costs [10,16]; however, they have ignored productivity losses. Galani et al. [17] mentioned that cost estimates included indirect costs, but they did not elaborate further on the consequences of this for the interpretation of their results. Nevertheless, most guidelines that recommend using a societal perspective also suggest comparing the results from two perspectives. Such a comparison has been usually missing from the studies. The review by Yokota and Thompson [2] highlights that in other sectors...
also applications have often chosen a relatively narrow perspective. Hence, to the best of our knowledge, only very few articles have included productivity losses and if they did, the implications were not thoroughly discussed. This seems an omission because in interventions that target chronic diseases with a high prevalence among patients in their working ages, productivity costs may have a large impact on cost-effectiveness results. Furthermore, productivity costs often can be estimated only with large uncertainty. Information on individuals’ working hours as well as hourly productivity may be difficult to ascertain and is not often included in most clinical trials. Therefore, looking at the impact of the choice of perspective and inclusion of productivity costs on the outcomes of a VOI analysis is worthwhile and was the aim of the current study.

A case study was chosen in the field of mental disorders. Many reports show that mental disorders lead to a reduction in employee productivity due to absenteeism or impaired functioning at work [18]. Depression is one of the major mental disorders with a high burden of disease [19,20]. Because of work loss, absenteeism, and presentism, productivity losses resulting from depression are considerable [21]. A recent study showed that productivity costs, on average, reflect more than half of the total costs for the treatment of depressive disorders [22]. In fact, the majority of costs of depression fall outside the health care sector; that is, the benefits of preventing depression are not restricted to the health sector but society as a whole. Accordingly, for many health care decision makers it will be relevant to consider a societal perspective in addition to the health care perspective in evaluating cost-effectiveness in depression prevention. Still, to date, most economic evaluations of treatments for adults with depressive disorders have ignored productivity losses [22].

The objective of our study then was to perform a VOI analysis in cost-effectiveness evaluation of preventing major depression (MD) in patients with minor depression. We considered both a societal and a health care perspective and paid attention to the consequences of different perspectives for policy advice. The depression case serves as an illustration for many interventions with large but uncertain effects on productivity costs.

Materials and Methods

In a recent study [23], a Markov model based on Vos et al. [24] was used to evaluate the costs and long-term health benefits of screening followed by minimal contact psychotherapy (MCP) for depression prevention. The model was adjusted to allow evaluation of depression prevention and was adapted to the Dutch setting. The short-term outcomes of MCP were previously evaluated alongside a randomized controlled trial [23]. The current article adds an elaborate VOI analysis and focuses on a comparison between the values of solving uncertainties for different perspectives. The model was used to extrapolate the trial outcomes over a 5-year time horizon. Five years were considered long enough to capture the full effects of the intervention and still short enough to trust the data on the population and the screening results. The discount rates used were 1.5% and 4% according to the Dutch Guidelines for pharmacoeconomic research [25], and monetary outcomes were valued in euros, at the 2008 price level. For clarity reasons, we explain the intervention, the model, and parameter estimation sources in the following sections.

Intervention

The intervention was opportunistic screening for subthreshold depression followed by MCP. Full details about the intervention and its short-term effects compared with no screening have been published before [26]. In short, opportunistic screening takes place in three steps: first, people are approached by the assistant when they are in the waiting room during a regular general practitioner visit. Those who are eligible for screening and give informed consent (participation rate 72.5%) are then screened for subthreshold depression (screen positive rate 26.6%). In a second step, screen-positive patients are approached for a further screening to check whether they meet the inclusion criteria for subthreshold depression (participation rate 35.7%). Those who meet all inclusion criteria receive MCP (59.5% of positive screens).

MCP consists of a self-help manual with instructions on cognitive-behavioral self-help in mood management skills. The manual contains registration exercises and homework assignments aimed at cognitive restructuring, relaxation, and activity scheduling to increase pleasant activities.

In the control group, no screening took place. People with subthreshold depression received care as usual from their general practitioner; that is, they were offered treatment on presenting themselves with symptoms.

The effects of the intervention were twofold: incidence and recurrence of MD decreased by 6% [26] and the total annual per-capita costs decreased by 21% [21].

Patient Population

The intervention targets patients with minor (subthreshold) depression. Subthreshold depression, which is diagnosed when a patient has two to four symptoms of MD, has a lifetime prevalence of 10% [27]. People with minor depression have an increased risk of developing MD compared with those not meeting the criteria of subthreshold depression [28].

Markov Model

The model distinguishes three main states: subthreshold depression, MD, and recovered from depression (no MD). Each state is divided into episodes that last for 4 weeks. After each cycle of 4 weeks, a person has the chance of moving to another state of disease, or to stay in the same state and start a new episode within that state. The Markov model is depicted in Figure 1.

The probability of developing MD for people with subthreshold depression (the incidence rate) has been assumed to be independent of the time that persons were in the subthreshold state, while the probabilities of recovery from MD and relapse into MD by assumption decreased over the time that was spent in MD and no-MD states, respectively. Parameters related to costs and quality-adjusted life-years (QALYs) in the recovered states are by assumption the same as in the subthreshold states.

Modeling and analyses were all done by means of the R software environment for statistical computing.

Parameter Estimation

Estimates of relapse and recovery rate as a function of duration were based on the Dutch NEMESIS study [19], a large population-based cohort study addressing mental disorders. The time-dependent probability curves for relapse and recovery rates can be found in van den Berg et al. [23]. Prevalence of subthreshold depression, intervention costs, and health care and societal costs for subthreshold depression were based on trial results [21]. Population parameters and incidence probabilities from subthreshold depression to MD were taken from Willems et al. [26]. Costs and productivity losses for MD were estimated on the basis of a review of Dutch studies [29–31]. QALY estimates were based on the NEMESIS study [19]. Distribution functions were estimated for all important model parameters. Parameters that were used in the probabilistic sensitivity analysis are presented in Table 1.

Effects of MCP were conservatively assumed to cease 1 year after the intervention. That is, after 1 year, persons are assumed to return to the same risk of developing MD as under care as usual if still in the subthreshold state.
Expected Value of Perfect Information

The expected value of perfect information (EVPI) was calculated for a cost-effectiveness range of 0 to 60,000 €/QALY. The global EVPI was computed as the difference between the expected net benefit of perfect and current information over a sufficient number of simulations, and the net benefits of the standard therapy (no MCP) were assumed to be zero:

\[ EVPI = E_\theta \max_c \{0, NB(MCP, c)\} - \max_c \{E_\theta NB(MCP, c), 0\} \]

Here \( \theta \) represents a list of unknown parameters. Population EVPIs were then computed by multiplying global EVPIs by the relevant population sizes. These were based on the prevalence of subthreshold depression [21].

In addition to this, parameters were grouped to find the expected value of perfect parameter information (EVPPPI) for each of these groups of parameters. EVPPPI or partial EVPI is intended to inform research priorities, that is, the type of additional evidence of these groups of parameters. EVPPI or partial EVPI is intended to estimate the maximum value of additional information on the value of this group of parameters and the expected value with current information on that group of parameters. It reflects the maximum value of additional information on the value of this group of parameters and may serve to help decide whether certain research to find better information on the parameters is worth its costs:

\[ EVPPPI_{\phi} = E_\phi \max_c \{0, NB(MCP, \phi, c)\} - \max_c \{E_\phi NB(MCP, \phi, c), 0\} \]

where \( \phi \) is the group of parameters of interest and \( \psi \) represents the remaining uncertain parameters. To compute the partial EVPI, first the simulation must be run for parameters \( \psi \) but with a particular value of \( \phi \) (an inner loop) and then a new value of \( \phi \) is sampled and the simulation is run again (an outer loop). This process is repeated until we have sampled sufficiently from the distribution of \( \phi \) [32].

Number of Simulations

Careful selection of the number of simulations needed in the inner and outer loops is required to balance off computation time and precision. The number of sufficient inner and outer loops for the EVPIs was computed by using a three-stage algorithm that estimates the bias and confidence intervals for the outcomes of EVPPI [33]. Predicted bias and the width of 95% confidence intervals for different number of inner loops (J) and outer loops (K) are presented in Table 2 for the health care perspective. The numbers presented are relative values, indexing the global EVPI (43,500,000 €) to 100. We chose \( J = 1000 \) and \( K = 100 \) as the sufficient numbers for our simulation from both perspectives because the bias was reasonably low and also the width of the confidence interval was estimated to be low enough at 3% of the global EVPI.

Results

Estimates of effects and costs per intervention together with incremental effects and costs are shown in Table 3. From a health care perspective, the incremental cost-effectiveness ratio of MCP compared with the standard therapy (no MCP) is about 1100 €/QALY. From a societal perspective, the intervention is cost saving [23].

We illustrate our results showing outcomes for two different perspectives in single pictures/graphs with the cost-effectiveness threshold on the horizontal axis, allowing a comparison of the societal and health care perspectives.

EVPPI

Figure 2 depicts the cost-effectiveness acceptability curves (CEACs) together with results of EVPI from a societal perspective and a health care perspective. CEACs were also presented by van den Berg et al. [23], but are repeated here to support explanation of the EVPI.

From a health care perspective, at low cost-effectiveness thresholds, prevention by using MCP is not cost-effective. The value of perfect information is relatively low because the decision not to implement MCP is relatively certain to be the best decision. The EVPI rises to a maximum of 57 million euros at a threshold value of about 1100 €/QALY, which is equal to the mean cost-effectiveness of the intervention from a health care perspective. For larger thresholds, the probability that the MCP is cost-effective increases and the EVPI decreases with the threshold rising. At a threshold surpassing the mean incremental cost-effectiveness ratio, we expect the intervention to be cost-effective and the decision is less likely to be changed by further information. With increasing cost-effectiveness thresholds, the value paid for each additional QALY increases. Hence, at high
Table 1 – Distributions of the parameters of intervention used in PSA (the EVPPI group indicates how the parameters were grouped for the partial value of information analysis).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No MCP</th>
<th>MCP</th>
<th>EVPPI group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Distribution</td>
<td>Mean (SE)</td>
<td>Distribution</td>
</tr>
<tr>
<td>Screening process</td>
<td>Fraction of the target population that agrees to be screened [26]</td>
<td>Beta distribution (z = 21; $\beta = 90$)</td>
<td>0.016 (0.003)</td>
</tr>
<tr>
<td></td>
<td>Fraction of screened included for diagnostic interview [26]</td>
<td>Gamma distribution (shape = 15; scale = 108)</td>
<td>1627 (419)</td>
</tr>
<tr>
<td></td>
<td>Fraction of interviewed included in intervention [26]</td>
<td>Gamma distribution (shape = 22; scale = 300)</td>
<td>6481 (1393)</td>
</tr>
<tr>
<td>Subthreshold states</td>
<td>Incidence probabilities from subthreshold to major depression [26]</td>
<td>Beta distribution (z = 21; $\beta = 90$)</td>
<td>0.016 (0.003)</td>
</tr>
<tr>
<td></td>
<td>Health care costs [21]</td>
<td>Gamma distribution (shape = 15; scale = 108)</td>
<td>1627 (419)</td>
</tr>
<tr>
<td></td>
<td>Productivity loss [21]</td>
<td>Gamma distribution (shape = 22; scale = 300)</td>
<td>6481 (1393)</td>
</tr>
<tr>
<td></td>
<td>Direct nonmedical costs [21]</td>
<td>Gamma distribution (shape = 43; scale = 12)</td>
<td>507 (77)</td>
</tr>
<tr>
<td>Major depression states</td>
<td>Quality of life [19]</td>
<td>Uniform distribution (0.81–1)</td>
<td>0.91 (0.05)</td>
</tr>
<tr>
<td></td>
<td>Health care costs [29–31]</td>
<td>Gamma distribution (shape = 15; scale = 152)</td>
<td>2280 (589)</td>
</tr>
<tr>
<td></td>
<td>Productivity loss [29–31]</td>
<td>Gamma distribution (shape = 8; scale = 27)</td>
<td>216 (76)</td>
</tr>
</tbody>
</table>

EVPPI, expected value of perfect parameter information; MCP, minimal contact psychotherapy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-years; SE, standard error.
values of the threshold, the global EVPI rises again because of an increased investment risk.

In contrast, from a societal perspective, the intervention is cost saving on average and the probability of a correct decision is always increasing as the threshold gets higher; hence, the global EVPI is always decreasing. We expect, however, that at very high thresholds (which are not shown in these graphs), the EVPI starts to rise, because high threshold values mean that a wrong decision is extremely costly.

It is apparent that the VOI is mostly higher from a societal perspective than from a health care perspective. Toward the right end of the willingness-to-pay scale, however, the VOI from the health care perspective rises above the levels of the EVPI from a societal perspective. This can be explained by having a look at the CEAC: it shows that the probability of making an incorrect decision remains higher for the health care perspective. Comparisons, however, of the VOI for different perspectives might require different willingness-to-pay thresholds. The amount that the decision maker is willing to pay per additional QALY would most likely change when different perspectives are considered. Therefore, to reach the best comparison, the values of the thresholds relevant for the decision makers should be known. For instance, if the threshold for evaluating MCP from a health care perspective is 20,000 €/QALY and the threshold for the same intervention from a societal perspective is 40,000 €/QALY, then the CEACs and EVPIs must be compared on two different points of 20,000 and 40,000 €/QALY on the x-axis. The vertical lines in Figure 2 show the comparison considering these hypothetical threshold values. We will come back to this point in discussion.

Partial EVPI

The EVPI for separate parameters groups from the societal perspective is illustrated in Figure 3. Results indicated that when the societal perspective is considered, the productivity loss was the most important source of uncertainty at any threshold. The effect of productivity loss, however, was more important for low

| Table 2 – Predicted bias and 95% CI for Monte Carlo partial EVPI estimate [33], EVPI indexed to 100. |
|-----------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| J = 10                                  | J = 100         | J = 500         | J = 1,000       | J = 5,000       | J = 10,000      |
| Bias (independent of K)                 | -7.62           | -0.54           | -0.21           | -0.05           | 0.03            | -0.09           |
| 95% CI                                  | 0.54             | 24.82           | 17.95           | 11.1            | 5.2             |
| K = 10                                  | 303.74          | 56.63           | 24.82           | 17.95           | 11.1            | 5.2             |
| K = 100                                 | 35.94           | 10.14           | 4.5             | 2.94            | 1.51            | 0.83            |
| K = 500                                 | 7.16            | 2.02            | 0.9             | 0.59            | 0.3             | 0.17            |
| K = 1,000                               | 3.58            | 1.01            | 0.45            | 0.29            | 0.15            | 0.08            |
| K = 5,000                               | 0.72            | 0.2             | 0.1             | 0.06            | 0.03            | 0.02            |
| K = 10,000                              | 0.35            | 0.1             | 0.05            | 0.03            | 0.01            | 0.01            |

CI, confidence interval; EVPI, expected value of perfect information.

| Table 3 – Estimates of effects and costs per intervention and incremental effects and costs. |
|-----------------------------------------|-----------------|-----------------|-----------------|
|                                        | QALYs x(1,000) | Health care costs x(1,000,000) | Total costs x(1,000,000) |
| No MCP                                 | 1,158          | 2,911           | 11,612           |
| MCP                                     | 1,170          | 2,924           | 11,240           |
| Incremental                             | 12             | 13              | -372             |

MCP, minimal contact psychotherapy; QALY, quality-adjusted life-year.

Fig. 2 – (a) Global expected value of perfect information (EVPI) curves; and (b) Cost effectiveness acceptability curves.
as population and recovery-relapse rates, were not significantly affecting the VOI, indicating that they would have a low priority in further research.

Results of the partial EVPI from a health care perspective are shown in Figure 4.

The partial EVPI graph indicated that the most important sources of uncertainty were health care costs. Because health care costs had such a clear effect on the uncertainty of the problem, they have been subdivided into two groups of parameters: health care costs in subthreshold depression and in MD. At very low thresholds, costs of MD were more important than at high thresholds. The health care costs of MD had an almost negligible expected VOI at thresholds above 5000 €/QALY. The incidence rate also had a considerable impact at low thresholds, but a low impact at high thresholds. Results showed that the most important priorities in future research were those related to the health care costs of subthreshold depression. The population that will finally receive the MCP also became an important parameter at high willingness-to-pay thresholds. This parameter is determined by the fraction of the target population that agrees to be screened, fraction of screened included for diagnostic interview, and fraction of interviewed included in intervention. Other parameters, related to QALYs, recovery rates, and relapse rates, were of very little importance in the health care perspective.

Discussion

This article examined how the VOI would change for different perspectives. The case study was the decision whether to use opportunistic screening in combination with MCP to reduce the incidence of MD. For depression, absence from work and the associated productivity costs represent an important part of the burden of disease. For this reason, results were evaluated both from a societal perspective and from a health care perspective. We found that regardless of the perspective, parameters related to costs had the largest EVPIs; that is, resolving their uncertainty would be most valuable for this case study. From a societal perspective, however, productivity costs got priority, while these were by their very nature ignored from a health care perspective.

The current case study could be illustrative for many other mental disorders: often productivity costs represent a relatively large part of the disease burden, and they are also often relatively uncertain due to a lack of data. It is obvious that when the societal perspective is relevant for the decision maker, a VOI from a health care perspective may lead to erroneous priorities for further research, especially in the presence of large and uncertain productivity costs.

Comparing the cost-effectiveness results from a societal perspective to a health care perspective as required by most guidelines recommending a societal perspective indicates that including societal costs in the analyses may significantly affect the outcomes and even change the decisions. The changes occur regarding not only the acceptability of the intervention but also priorities for further research and VOI. According to the cost-effectiveness acceptability curves (Fig. 2), for very low willingness-to-pay thresholds, from a health care perspective rejecting the intervention seems to be the most reasonable decision. From a societal perspective, however, for low thresholds, accepting the intervention has a fair chance of being cost-effective.

To have an estimation of the EVPI, we look at the graphs at the unofficial Dutch thresholds for preventive interventions of 20,000 €/QALY [34]. This threshold was first mentioned in a health care perspective setting [35]. It has also been used, however, for analyses in a societal perspective [34]. At the threshold of 20,000 €/QALY, the global EVPIs had a value of about 42 and 32 million euros from societal and health care perspectives, respectively, both indicating that it would be worthwhile to gather more information.

Hence, using an invalid perspective could lead to unrealistic importance attached to additional research, depending on the actual threshold value. As mentioned in the “Results” section, however, considering the same threshold for both perspectives is not very practical. In real-world decisions, threshold values change on the basis of the perspective chosen. From a societal perspective, threshold values should reflect the consumption value of health, while from a health care perspective they would reflect the marginal value of health provided for by a publicly financed health care system, which are not necessarily the same. Opinions differ, however, on this issue [14,36]. Meanwhile, it is not clear how large the difference between the two thresholds...
should be. In applications, similar threshold values are sometimes mentioned in studies applying a societal perspective as well as studies using a health care perspective. For instance, as mentioned before, the unofficial Dutch threshold of 20,000 €/QALY has been used in both health care and societal perspectives, indicating the difficulties in understanding the relationship between perspective and threshold in many decision contexts.

We chose to illustrate our results in graphs with a single threshold on the x-axis. If the actual thresholds were larger from a societal perspective (following the reasoning in Claxton et al. [14]), then a figure that compares both perspectives should use two different scales on the x-axis, effectively shifting the societal perspective graph to the left. This implies that the differences between the societal and health care perspectives in the value of the global EVPI decrease. It is obvious that the only way to reach a precise comparison between the VOI from the two perspectives is to know the exact willingness-to-pay threshold considering each perspective.

Using a health care perspective, VOI analysis informs decision makers about allocating funding for actual interventions and research that basically can be considered as originating from the same health care budget. All costs and savings hence refer to the same budget and decision maker, even if in reality earmarking and separate budgets will be present. Using a societal perspective, however, this may no longer hold. For instance, savings in productivity costs will accrue to employers, not to health care decision makers. In recent years, this has led to discussions on how the costs of interventions and research must be sponsored when a societal perspective is considered. Debates are mostly focused on public health interventions, in which the impacts are often wide-ranging. Costs and benefits associated with an intervention aiming at public health, such as the depression prevention case, will fall on many sectors within the society [37]. Some authors just assume that when a societal perspective is taken, the society pays for health care interventions through a single payer system and also pays for research projects for reducing uncertainties through government or private donation-based agencies [38]. Weatherly et al. [37] reviewed a number of approaches that have been suggested to account for the impact of interventions across different sectors. For instance, Claxton et al. [39] introduce a multisectoral societal decision-making approach to evaluate costs and benefits that fall on different sectors of the economy. Smith et al. [40] also demonstrate the value of using a macroeconomic approach to modeling a major health problem, using the context of antimicrobial resistance and applying general equilibrium analysis. Following Willan and Pinto [38], it seems valid to argue that a societal perspective implies that resources can—in principle—be transferred from one part of the economy to the other and the extended Pareto criterion may be applied to decide whether an intervention or additional research is worthwhile. Hence, in the presence of uncertainty, VOI analysis will inform whether additional research is potentially worthwhile from a societal point of view to support better future decision making, independent of who is going to pay or gain from this research.

To conclude, our results underlined the need for carefully choosing the relevant perspective for the decision problem at hand, also in VOI analyses, to avoid erroneous choice of research priorities.

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