Embracing uncertainty in health technology assessment

Summary

Reimbursement decisions concerning health care technologies are made under uncertainty because decision makers wish to rapidly make health care technologies available to patients while the evidence supporting these decisions is often immature and/or incomplete. As a consequence of this uncertainty, pharmaceuticals that do not provide value for money may be reimbursed, while pharmaceuticals providing value for money may not be reimbursed through health insurance packages. The aim of this thesis was to apply and develop methods to identify and assess uncertainty in health technology assessments (HTA). HTA aims at informing decision makers about the value of health care technologies through a systematic assessment of properties, effects, and/or impacts of these health care technologies.

Model-based health economic evaluations play a prominent role in reimbursement decisions because they facilitate data synthesis, data extrapolation, and allow to include all relevant comparators for the decision of interest. Health economic models further allow to assess the uncertainty surrounding the cost effectiveness of pharmaceuticals. One method used to assess the uncertainty surrounding health policy decisions is value of information (VOI) analysis. VOI analysis quantifies the impact of uncertainty (combining the probability and consequences of reimbursing a cost-ineffective health care technology) to provide an estimation of the risk associated with the decision at hand. Once the risk surrounding the decision is estimated, financial and/or outcome-based Managed Entry Agreements (MEAs) can be implemented to manage it. MEAs are agreements between payers and pharmaceutical companies aiming at providing access to a pharmaceutical while managing the uncertainty surrounding their (cost) effectiveness, and/or budget impact. Coverage with evidence development (CED) is a type of MEA during which a pharmaceutical is temporarily reimbursed and additional evidence is collected concerning its (cost) effectiveness. This additional evidence aims at taking a better-informed after the CED period. In the Netherlands, registries are a common CED research design. VOI is valuable for the design and prioritisation of further research because it can be used to provide information on which element(s) of the assessment further research should focus, to evaluate the value of potential research designs, and to identify the most optimal research design. VOI can contribute to the design of MEAs by estimating the impact of different MEAs on the risk of reimbursing pharmaceuticals.

The first part of this thesis describes how uncertainty is currently considered in reimbursement decisions. **Chapter 2** investigates which uncertainties were present before the initiation of CED research and whether these uncertainties were included in CED research plans. Stakeholders involved in these CED schemes were interviewed on issues and ways forward with uncertainty in CED schemes. In all three investigated

CED schemes, CED research designs focused on the set-up or continuation of registries to collect clinical data to inform reimbursement continuation. A systematic identification of uncertainty was lacking before CED research initiation and there was a poor relation between the uncertainties present before CED initiation and those included in the CED research plans. VOI analysis was performed in one case, but VOI results did not inform decision making. Stakeholders argued for more flexible CED research design which should be informed by uncertainties present before CED initiation. Stakeholders questioned whether CED research reduced the identified uncertainties. **Chapter 3** presents a review of the single technology appraisal concerning fluocinolone acetonide intravitreal implant for treating non-infectious uveitis of the posterior segment in the United Kingdom. This chapter describes which uncertainty influenced the cost-effectiveness results and the reimbursement decision during this appraisal. Prominent uncertainties concerned the place of fluocinolone acetonide in the treatment pathway, the definition and measurement of the primary outcome of the pivotal trial, and the absence of a relevant comparator (dexamethasone) in the company submission. Through scenario analyses, the evidence review group showed the impact on the results of considering dexamethasone as a comparator. The impact of other uncertainties, such as the place of fluocinolone in the treatment pathway, could not be assessed. The appraisal committee acknowledged the uncertainty surrounding the results. Considering the range of results, the appraisal committee concluded that fluocinolone was a cost-effective use of National Health Service resources. Fluocinolone acetonide intravitreal implant was recommended for treating non-infectious uveitis of the posterior segment.

The second part of this thesis focuses on applying different methods to assess uncertainty. All methods are applied to case studies considering the assessment of chemotherapy for the treatment of advanced breast cancer (ABC) patients. **Chapter 4** is a literature review of model-based health economic evaluations concerning ABC treatments. This chapter investigates the relation between study characteristics and study quality and outcomes. On average, the included studies satisfied 14 out of the 26 items of a well-known quality checklist. Items of the checklist were often not fulfilled due to a lack of transparency in reporting. No relation was found between study characteristics and outcomes, except that industry-sponsored analyses seemed to result more often in favourable outcomes for the intervention than studies performed independently of industry. In **Chapter 5,** the relative effectiveness of eribulin (a novel chemotherapy) versus non-eribulin chemotherapy for the treatment of ABC patients is estimated using data collected through the SOutheast Netherlands Advanced BREast cancer (SONABRE) registry (NCT03577197). Forty-five patients

received eribulin. Eribulin was administered as a late treatment line to most patients. Since registry data informed this study, uncertainty arose due to the absence of randomisation and the potential bias induced by confounding by indication. Genetic Matching was applied on treatment lines administered to patients to address this bias. Using treatment line matching, eribulin did not lead to a statistically significantly increased overall survival compared with non-eribulin chemotherapy (hazard ratio: 0.66, 95% confidence interval: 0.38-1.13). This study emphasised the tolerable toxicity profile of eribulin. **Chapter 6** builds upon **Chapter 5** and estimates the cost effectiveness of eribulin versus non-eribulin chemotherapy, using a health economic model. The budget impact and risk (estimated through VOI analysis) associated with reimbursing eribulin were also estimated. The estimated incremental cost-effectiveness ratio (ICER) was € 220,608 per quality-adjusted life-year gained versus non-eribulin chemotherapy. This ICER exceeds the Dutch willingness-to-pay thresholds. Uncertainty surrounding the results arose due to the limited number of patients receiving eribulin and the lack of health-state utility values estimated in patients receiving eribulin. Both budget impact and risk of reimbursing eribulin are limited, mainly because of the small estimated number of patients who may receive eribulin in the Netherlands.

The third part of this thesis focuses on developing methods and tools to improve the identification and assessment of uncertainty in HTAs. In **Chapter 7**, the development of the ParamEtRic SUrvivAl moDel sElection (PERSUADE) template is described. This template aims at supporting the selection of parametric survival models incorporated in health economic models and at rendering it more transparent and accessible. The PERSUADE template provides the necessary input to transparently justify which parametric survival model(s) is (are) the most plausible and may help to prevent mistakes in the implementation of parametric survival models in health economic models. This will potentially increase the consistency, transparency, internal validity, and consequently the credibility of the selected parametric survival models. **Chapter 8** describes a method to capture structural uncertainty stemming from survival model selection in health economic models by applying model averaging of the probabilistic sensitivity analysis (PSA) results of the health economic model developed in **Chapter 6**. This study outlines a method to compute weights for model averaging which considers both statistical fit information and clinical expert opinion. Ignoring survival model selection uncertainty led to biased cost-effectiveness results and uncertainty estimations. The value of reducing survival model selection uncertainty was estimated through VOI analysis. In this specific case, the value of reducing survival model selection uncertainty was low because all fitted parametric survival models led to approximately similar incremental survival estimates. This

result is likely case-specific and could be substantially different in other assessments. **Chapter 9** describes the development and validation of the TRansparent Uncertainty ASsessmenT (TRUST) tool. TRUST enables a systematic identification, assessment, and reporting of all uncertainty prevailing in all aspects (scope/context, model structure, selection of evidence, model inputs, model implementation, model outcomes) of a health economic model. TRUST highlights the source of uncertainty (transparency, methodology, imprecision, bias and indirectness, and unavailability) since different sources of uncertainty may call for different types of analyses and health policy decisions to manage these uncertainties. TRUST also provides a simple overview of uncertainties which are (not) included in the PSA and VOI analysis.

In the Netherlands, registries were implemented as part of CED schemes to regulate the uptake of expensive and specialised treatments between 2006 and 2012. These registries aimed at reducing the uncertainty surrounding the cost effectiveness of these treatments through data collection concerning their real-world clinical use, costs, and effectiveness. VOI, which can contribute to the design of MEAs, was not routinely used to inform the design of these registries. The general discussion of this thesis therefore focuses on two subjects: a) the importance of VOI analysis for health policy decisions, and b) the use of registries to inform health policy decisions. Regarding the importance of VOI analysis for health policy decisions, this thesis argued that not considering VOI analysis in health policy decisions has multiple negative consequences. By not considering VOI analysis results, decision makers are unaware of the risk they face and may thus not be able to adequately manage it. Also, research which is not worthwhile may be commissioned because the value of additional research is not investigated. Routinely considering VOI results is therefore warranted to inform health policy decision making. Implementing VOI in practice is however challenging because performing VOI analysis may be time consuming and it requires multiple stakeholders to interact with each other, ideally in an iterative way. More research is needed to determine how to implement VOI analysis in practice. Concerning the technical implementation of VOI, further research should focus on improving guidance on the implementation of model averaging, to ensure future VOI analysis provide more complete assessment of uncertainty than currently performed. Nevertheless, the ideal situation where all uncertainty surrounding a health policy decision is incorporated in VOI analyses may never be achieved for two reasons: a) we may not be aware of all uncertainty affecting a decision, b) health economic evaluations do not capture all aspects of value of pharmaceuticals because they operationalise value in cost per quality-adjusted life years gained. It is currently still unclear how these broader aspects of value of pharmaceuticals should be weighed against value for money in health policy decisions. If stakeholders desire to consider

these broader aspects of value in health policy decisions, a framework considering these indicators of value and their surrounding uncertainty should be developed.

Secondly, the use of registries to inform health policy decisions is discussed. We identified a disconnect between the uncertainties present before CED initiation and the ones included in CED research plans. A reason explaining this disconnect is the lack of systematic uncertainty identification before CED initiation. Consequently, CED research may not focus on the most important uncertainty for the decision. A systematic identification of uncertainty, through the use of TRUST for instance, is warranted to prevent that important uncertainty are overlooked and future registries focus on the most important uncertainty. Registries have several advantages above performing randomised controlled trials such as being cheaper and including patients who are representative of patients encountered in clinical practice. However, the analysis of registry data is challenging due to the absence of randomisation, potentially causing confounding by indication. Statistical methods have been developed to address this bias but analysis choices are often made ad hoc when the registry data has already been collected. Describing analysis choices a priori in a protocol may improve the design of registries and the analysis of registry data. Methodological guidelines should be developed to inform decision makers and researchers designing a registry about the available types of analysis, their (dis)advantages, and how to perform them.

In conclusion, the current thesis has argued that health policy decision making could be improved by a more systematic assessment of uncertainty and risk through a structured implementation of VOI analysis and the use of registry data. This thesis shows how registry data can be used to assess the (cost) effectiveness of a pharmaceutical, and provides a method and tools to improve uncertainty identification, assessment, and reporting during the assessment of health care technologies. Embracing uncertainty through the widespread adoption of the method and tools described in the current thesis may increase stakeholders' awareness about uncertainty and the opportunities that considering uncertainty in health policy decisions may create. These opportunities encompass a better management of risk, which would ultimately lead to greater health benefits being obtained with the available resources. Finally, it would increase the value of research that is performed to inform health policy decisions.