General introduction

BACKGROUND

On a global scale, Europe bears 25% of all estimated cancer cases worldwide, while accounting for only 9% of the world's population.[1] Simultaneously, cancer is the second leading cause of death after cardiovascular diseases in Europe, accounting for 26% of all deaths in 2016.[2]

Between 1995 and 2018, the incidence of cancer increased by approximately 50%, while mortality due to cancer increased with 20% during the same time span.[2] Consequently, the number of patients with cancer increased through the last decades. Identified reasons for this development are advances in cancer research covering screening, diagnostics, and medical treatment.[2–4]

As research efforts to reduce the burden of cancer continue, worldwide healthcare spending increases rapidly.[5] In Europe, health expenditure on cancer care were estimated at 103 billion EUR, of which 31% (i.e. 32 billion EUR) could be attributed to cancer drugs alone.[6] In fact, cancer medicines have been found to be particularly highly priced, both in absolute and relative (i.e. compared to other therapeutic areas) terms.[7] In addition, expenditure on cancer drugs increased at a higher rate than the incidence of cancer and overall health expenditure during the last two decades.[7]

Although healthcare *spending* on cancers increase, healthcare *resources* remain limited. Hence, funding novel treatments requires additional budget or funding will be at the expense of other treatments. This can lead to displacement effects (i.e. when novel treatments with less favourable cost-effectiveness are funded at the expense of treatments with a more favourable cost-effectiveness profile), and decision makers need to be aware of such opportunity costs.[8] The following dilemma may arise: novel treatments are needed to improve population health and well-being but reimbursing all of them will inevitably result in exceeding the financial capacity of a healthcare system. Therefore, novel treatments will no longer be affordable. And indeed, the 2020 drug monitoring report of the *Dutch Healthcare Authority* (Nederlandse Zorgautoriteit, NZa) concluded that in the Netherlands, the affordability of novel and expensive treatments is already at risk.[9] This holds true for most countries worldwide.[10–13]

To ensure the affordability of health care, reimbursement decision makers may use various approaches and many countries have adopted (elements of) value-based pricing for this purpose.[7] With such an approach, prices at which novel treatments are reimbursed are determined based on the value that patients and health systems perceive for the particular treatment.[7] A formal Health Technology Assessment (HTA) can aid in determining this value in a transparent and reliable way.

This dissertation explores the utilisation of HTA in the field of haemato-oncology with the aim of identifying and addressing challenges in assessing both costs and cost-effectiveness of

novel treatments in haemato-oncology. This chapter will briefly outline important concepts related to HTA, define the research objectives and describe the outline of this dissertation.

HEALTH TECHNOLOGY ASSESSMENT

The main aim of HTA is to inform decision-making in healthcare (e.g. on the reimbursement of a treatment) by incorporating a multidisciplinary approach and evaluating economic, organisational, social and ethical aspects of a health technology.[14] As such, HTA actively interprets medical evidence and puts it into context with the pertinent healthcare system.[15] Since its beginnings in the 1980s, HTA has often been (re-)defined.[16] A recent report of the *European Network for Health Technology Assessment* (EUnetHTA) defines nine domains of HTA which are interrelated and highlight the multidisciplinary aspect of HTA.[17] These domains are (1) *health problem and current use of technology*, (2) *description and technical characteristics of technology*, (3) *safety*, (4) *clinical effectiveness*, (5) *costs and economic evaluation*, (6) *ethical analysis*, (7) *organisational aspects*, (8) *patient and social aspects*, and (9) *legal aspects*.

This dissertation covers several of these aspects, while its main focus lies on identifying and addressing challenges in the domain of *costs and economic evaluation*. Since all of the defined domains are interrelated, other domains of interest in this dissertation are *safety*, *clinical effectiveness*, as well as *patient and social aspects*.

Economic evaluation

Economic evaluations assess both allocation and efficiency of resources to improve health outcomes or health care in general. Several methods of conducting economic evaluations exist including cost-benefit analysis, cost-effectiveness analysis (CEA), and cost-utility analysis (CUA). While the latter two aim at informing decision-makers on how to best allocate existing budget to maximise (health) outcomes, only CUAs incorporate health-related quality of life (HRQoL) in their outcome measures and are therefore preferred in most jurisdictions.[18] Since CUAs are an integral part of this dissertation, some important conceptual aspects will be outlined hereafter.

Cost-utility analysis

CUAs can critically appraise both incremental costs and effects of one treatment when compared to one or several other treatments.[19] In this way, decisions can be made on the basis of evidence rather than on "what was done before", "educated guesses", or "gut feelings".[19]

Several analytical perspectives are available to conduct CUAs. In the field of cancer, either a healthcare payer or a societal perspective is commonly adopted.[20] The chosen perspective depends to a large extent on the type of decision-maker intended to be informed and on recommendations issued by pharmacoeconomic guidelines of the respective jurisdiction.[19]

As the name already suggests, a *healthcare perspective* typically covers all effects and costs within the healthcare sector that are related to the prevention, diagnostics, pre-treatment, treatment, hospital stays, and follow-up care or rehabilitation of the technologies under investigation. However, since health economics is deeply rooted in welfare economics, a perspective that also covers the impact of the novel treatment on the welfare of the entire society is often recommended.[19,21–23] Such a *societal perspective* ideally covers both effects and costs not only within the healthcare sector, but includes patient and family aspects as well.[21,19,24] Regarding effects, a societal perspective may go beyond the patients' health and HRQoL to include for instance care-related quality of life of caregivers, when appropriate.[25] Regarding costs, a societal perspective typically also covers costs for patients and their families. Examples are for instance costs from out-of-pocket expenses, informal care, or loss of productivity due to illness.[19]

Since most pharmacoeconomic guidelines prefer a lifetime horizon on costs, so-called "future costs" should be considered as well.[19,26] These can be divided into related or unrelated medical costs and non-medical consumption costs. The former includes costs for follow-up visits or treating diseases that are related or unrelated to the disease for which the intervention is assessed. The latter are defined as costs of consumption (e.g. food and living) minus production (e.g. work during life years gained). However, since most pharmacoeconomic guidelines do not explicitly mention the inclusion of future non-medical consumption costs, the impact of these costs on the results of economic evaluation studies remains understudied.[26,27]

Generally, CUAs can either be conducted alongside clinical trial studies (also referred to as "piggyback studies"[28]) or as decision-analytic models. In the latter case, evidence from a variety of different sources can be integrated into the analysis.[29] However, this requires an extensive synthesis of all necessary model input parameters on both effects and costs. While methodological aspects of most steps for conducting CUAs are well documented, synthesising evidence on both effects and costs probably remains one of the most challenging aspects. Therefore, the step of synthesising evidence for HTA in general and CUAs in particular will be introduced in more detail below.

SYNTHESISING EVIDENCE FOR HEALTH TECHNOLOGY ASSESSMENT

Research questions in the *costs and cost-effectiveness* domain of HTA can be answered in two ways. First, existing evidence, including published economic evidence or existing economic evaluations submitted for reimbursement decisions, can be searched and reviewed systematically.[17] Second, new evidence can be generated by conducting *de novo* economic evaluations.[17]

Synthesising evidence from published economic evaluations

Critically appraising already available evidence can be useful for several reasons. It reveals what is already known, points to what is still unknown, and can reveal knowledge gaps about economic aspects of a given topic.[30] Searching for economic evidence in a systematic and standardised way ensures that no relevant information is missing or left out due to methodological biases. To aid in systematically synthesising published economic evaluations, the *Centre for Reviews and Dissemination* (CRD) published a guidance in 2009.[31] This guidance suggests searching the *NHS Economic Evaluation Database* (NHS EED) and the *Health Economic Evaluations Database* (HEED) to identify economic evaluation for systematic literature reviews (SLRs). Also the *Cochrane Handbook for Systematic Reviews of Interventions* recommends the use of the NHS EED database to search for economic evidence.[32] However, the HEED is no longer accessible since 2014, and the NHS EED is no longer updated since 2015. Consequently, researchers and policy makers need to rely on biomedical databases, to find relevant information. Since these databases primarily index biomedical literature, indexing economic literature is not in their focus. This makes the detection of health economic evidence a challenging task.

While guidance exist on conducting SLRs, this guidance is fragmented, not always specifically aimed at finding economic evaluations, or not detailed.[30] Without a comprehensive and uniform guidance, it cannot be ensured that reviews of economic evaluations are conducted in a reliable and systematic way.

Synthesising evidence on effects

To fulfil the criteria of evidence-based medicine, observations from randomised controlled trials (RCTs) regarding benefits and harms of (novel) treatments are seen as best available research evidence.[33,34] Typically, RCTs are conducted after a series of clinical studies with different goals and objectives. Classically, these studies are referred to as clinical trials and have been divided into phases I through IV.[35] Due to the relatively larger patient population and an extended follow-up time when compared to phase I-II studies, RCTs are often self-evidently presented as the "golden standard" of establishing safety and efficacy.[36] Therefore, RCTs are often used to inform both the *safety* and *clinical effectiveness* domains of HTA. However, the use of phase II clinical data for HTA has increased lately. This is mainly due to efforts to improve a timely access for patients to novel treatments, especially in cancer care. After all, clinical trials in oncology last on average 40% longer when compared to other therapeutic areas.[37]

To what extent data from phase II clinical studies can be used to conduct CUAs, especially when novel and expensive treatments may have potential curative effects, has initiated a recent debate.[38] Also, it is yet unclear how useful such data can be to conceptualise and run decision models.

Synthesising evidence on costs

Generally, costs are calculated by multiplying quantity and price. In health care, quantity often refers to resource use. For instance, the number of tablets a patient ought to receive during treatment or the number of days a patient spends at the hospital during a treatment. To derive costs, this quantity is multiplied with the price for one tablet of the treatment or the price for one day at a hospital. Depending on the chosen health-economic perspective, many other types of resource use such as travel time to the hospital or hours of informal care may be of interest.

Challenges in synthesising evidence on costs may arise for both measuring resource quantity and valuing it with a respective unit costs or price. To gather evidence on resource use, RCTs might be an obvious source of information as they already closely follow patients during the study time. Items related to a healthcare perspective such the number of hospital days or type and amount of medication administered are often already recorded and should therefore be readily available. However, since clinical trials have a limited follow-up period and employ rather strict in- and exclusion criteria, the collected evidence might not be easily transferrable to the entire patient population. In addition, trial data are rarely made publicly available to a degree that would allow its use for further analyses.[39]

Alternatively, information on resource use could be synthesised from costing studies, patient questionnaires, or electronic patient dossier.[19,40–42] However, on the one hand, costing studies from a preferred bottom-up, micro-costing approach are very time consuming and often not feasible. On the other hand, self-reported utilisation of resource showed to be of variable accuracy and underreporting seems to be a frequent issue with this methodology.[43]

Good quality electronic patient records *per contra*, could be used not only to prompt better care, improve coordination of care, or monitor the health of populations.[44] They could also be used to conduct research,[44] including the evidence synthesis on costs. This is because (parts of) these records are often used to inform financial claims from the hospital to the health insurers. Hospitals are therefore well-advised to maintain a detailed administration of all patient related activities to be able to claim costs for those activities.

Such a database would lend itself for gathering information on healthcare resource use.

THE COST-UTILITY OF NOVEL TREATMENTS IN HAEMATO-ONCOLOGY

As stated earlier, prices for cancer drugs in general are high and increasing throughout the last decades. And since the treatment of haematological malignancies heavily relies on drugs, the field of haemato-oncology is markedly affected by this trend.[45] Indeed, of all 88 newly approved oncologic therapies by the US *Federal Drug Administration* (FDA) between 2012

and 2018, approximately 32% (N =28) targeted haematologic malignancies.[46] In contrast, these malignancies account for approximately 8% of the global incident cases of all cancers.[47]

In 2016, the first population-based cost analysis of malignant blood disorders across Europe estimated the total costs of these disorders to be 11.3 billion EUR in 2012.[48] Expenditure on drugs (i.e. antineoplastic drugs and endocrine treatment) accounted for 1.9 billion EUR (17% of total costs).[48] While "old" drugs such as cyclophosphamide are rather inexpensive, it seems that an increasing number of novel high-priced drugs for haematologic malignancies are flooding the market, especially in recent years.[45] Examples for such treatments are immunomodulatory agents such as lenalidomide with mean monthly therapy costs between 2,049 EUR (second treatment line; 2009 Euro) and 3,651 EUR (fourth treatment line; 2009 Euro) per patient.[49] More recently, chimeric antigen receptor (CAR) T-cell immunotherapies such as tisagenelecleucel with a list price of 320,000 EUR per patient received central marketing authorisation by the EMA.[50,51]

Determining the cost-utility of these treatments through formal CUAs is important to enable reimbursement decisions on scientific evidence.

IMPLICATIONS OF CUAS ON HEALTHCARE DECISION-MAKING

Once the *European Medicines Agency* (EMA) has granted central marketing approval for a novel treatment based on the safety and efficacy profile of a novel treatment, pricing and reimbursement decisions fall within the competency of each Member State. This means that every payer (i.e. insurance companies or the state) needs to negotiate or set a price at which the respective treatment is reimbursed. HTAs play an important role in the reimbursement decision-making in many countries worldwide. Several European countries have therefore established institutions or organisational bodies dedicated to the evaluation of healthcare technologies. While national agencies operate differently across countries, they usually share a set of basic objectives and structures. Generally, they either take on an advisory or a regulatory role in the reimbursement decision-making process.[52] By means of two example, the differences between these roles will be clarified below.

HTA advisory bodies: an example

In the Netherlands, the *National Health Care Institute* (Zorginstituut Nederland, ZIN) has a mandate to safeguard the accessibility, affordability and quality of healthcare. As such it has an advisory role and makes reimbursement and pricing recommendations to the Minister of Health, Welfare and Sport.

Since 2015 the Dutch government makes use of a lock (Dutch: *sluis*) system for novel and expensive treatments. Once a medicine is placed in the lock, it is temporary excluded

from the basic health insurance package and hence not reimbursed by the health insurance. The drug manufacturer can submit a reimbursement dossier to the ZiN which then assesses the medicine on the criteria of necessity (how high is the disease burden for patients?), effectiveness (how effective is the medicine?), cost-effectiveness (what is the price of the medicine with regards to its value for the patient?), and practicability (is the inclusion of the drug into the basic insurance package realistic in practice?).[53] This assessment is based on a pharmacoeconomic dossier (commissioned) by the manufacturer. In case of a positive assessment, the ZIN advises the Minister of Health whether price negotiations with the drug manufacturer are necessary. Such price negotiations are usually confidential. Finally, the Minister of Health takes a definitive decision on whether the medicine shall be added to the basic health insurance package.

HTA regulatory bodies: an example

In the UK, the *National Institute for Health and Care Excellence* (NICE) has a regulatory role and is accountable to the Ministry of Health. It is responsible for conducting HTA on behalf of the *National Health Service* (NHS).[52] In 2017, the NICE framed three strategic objectives.[54] One of which is centred around providing evidence and guidance to provide high quality care that makes efficient use of resources.[54] Following this objective, the NICE conducts so-called technology appraisals on the use of new and existing medicines and treatments within the NHS. Such appraisals are based on both clinical and economic evidence.[55] Once the NICE has issued a positive recommendation, the NHS is legally obliged to fund and resource the respective medicine or treatment.[55]

As can be seen from the two examples above, jurisdictions tend to integrate evidence synthesised through formal HTAs differently into their reimbursement processes. It is therefore important to interpret outcomes of such assessments (especially the cost and cost-effectiveness domain of HTA) within a country-specific context.

CHALLENGES IN ASSESSING COSTS AND COST-EFFECTIVENESS OF TREATMENTS IN HAEMATO-ONCOLOGY

In the previous paragraphs, three key elements of HTA have been outlined and (potential) challenges in each of those were briefly sketched.

First, the evidence synthesis of clinical efficacy and health-economic information (in the form of costs and cost-effectiveness) are core components of each HTA. However, systematically searching published cost-effectiveness analyses has become more challenging since health economic databases seized to exist, and challenges in synthesising information on

the cost of healthcare based on hospital financial claims databases are not extensively documented. In addition, it is not fully explored in how far previously published phase II clinical data can be used to inform the building of a decision model that summarises this evidence.

Second, several novel and expensive haematological treatments such as tisagenlecleucel and lenalidomide demonstrated favourable efficacy results versus the studied comparator treatment and have recently received marketing approval by the EMA. However, results from cost-utility analyses are needed to make evidence-based reimbursement decisions.
Third, the advisory or regulatory role of HTAs in the reimbursement decision-making process in several European countries is well documented in its theory. However, to what extent specific assumptions made in CUAs can affect reimbursement decisions, or whether outcomes of CUAs on novel and expensive haematological treatments are actually used to form decisions is less known. In addition, the future financial impact of expensive haematological treatment options with potential curative effects on healthcare systems in Europe is not yet fully understood.

Identifying and addressing these issues and challenges were the motivation to write this dissertation.

OBJECTIVES AND OUTLINE

The aims of this dissertation are to identify and address several challenges arising in assessing costs and the cost-effectiveness of interventions in haemato-oncology. In addition, the cost-effectiveness of two novel and expensive treatment options for haematological malignancies will be assessed.

To work towards these aims, this dissertation is structured into three parts. The first part addresses various challenges of the evidence synthesis for the *costs and economic evaluation* domain of HTA. The second part assess the cost-utility of two novel and expensive haematological treatments. The third part describes challenges in the reimbursement decision-making process based on HTA.

PART I includes **Chapters 2 to 4** which explore and address *challenges in the evidence synthesis* for HTA. **Chapter 2** addresses the challenge of systematically finding previously published economic evidence. It aims at determining a transparent and reliable methodology for collecting published economic evidence for HTA. In the absence of evidence on the healthcare resource use and costs of paediatric patients with sickle cells disease in the Netherlands, **Chapter 3** explores to what extent hospital financial claims data can be used to estimate these costs. Since phase II clinical data are increasingly used for reimbursement decision making, **Chapter 4** assesses to what extent published phase II individual patient level data can be used in *de novo* decision models and CUAs.

PART II comprises **Chapter 5 to 6** and aims at providing *evidence on the cost-utility* of novel and expensive treatments in the field of haemato-oncology. In addition, it aims at examining the impact of expanding a societal perspective in CUAs to include future non-medical consumption costs on the ICER. **Chapter 5** assesses the cost-effectiveness of the CAR T-cell therapy tisagenlecleucel for the treatment of paediatric patients with relapsed or refractory B-cell ALL. **Chapter 6** assesses the cost-effectiveness of rituximab in combination with lenalidomide for patients with previously treated follicular lymphoma.

PART III of this dissertation includes **Chapters 7 to 8** and describes *implications of CUAs on healthcare decision-making*. Furthermore, it investigates the impact of expensive immunotherapies for the treatment of cancer on (future) healthcare expenditures in Europe. **Chapter 7** describes how results of CUAs can lead so-called "restricted decision" to reimburse novel and expensive anti-cancer treatments. **Chapter 8** provides a forecast on healthcare expenditures of current and novel CAR T-cells therapies for the treatment of haematological cancers in Europe.

Finally, in **Chapter 9** the main findings of this dissertation are summarised, discussed and interpreted in the context of research and policy. In addition, recommendations for further research and healthcare policy are provided.

Note that **Chapters 2 to 8** are based on publications in, or intended for, international peer-reviewed journals and can therefore be read as independent papers.