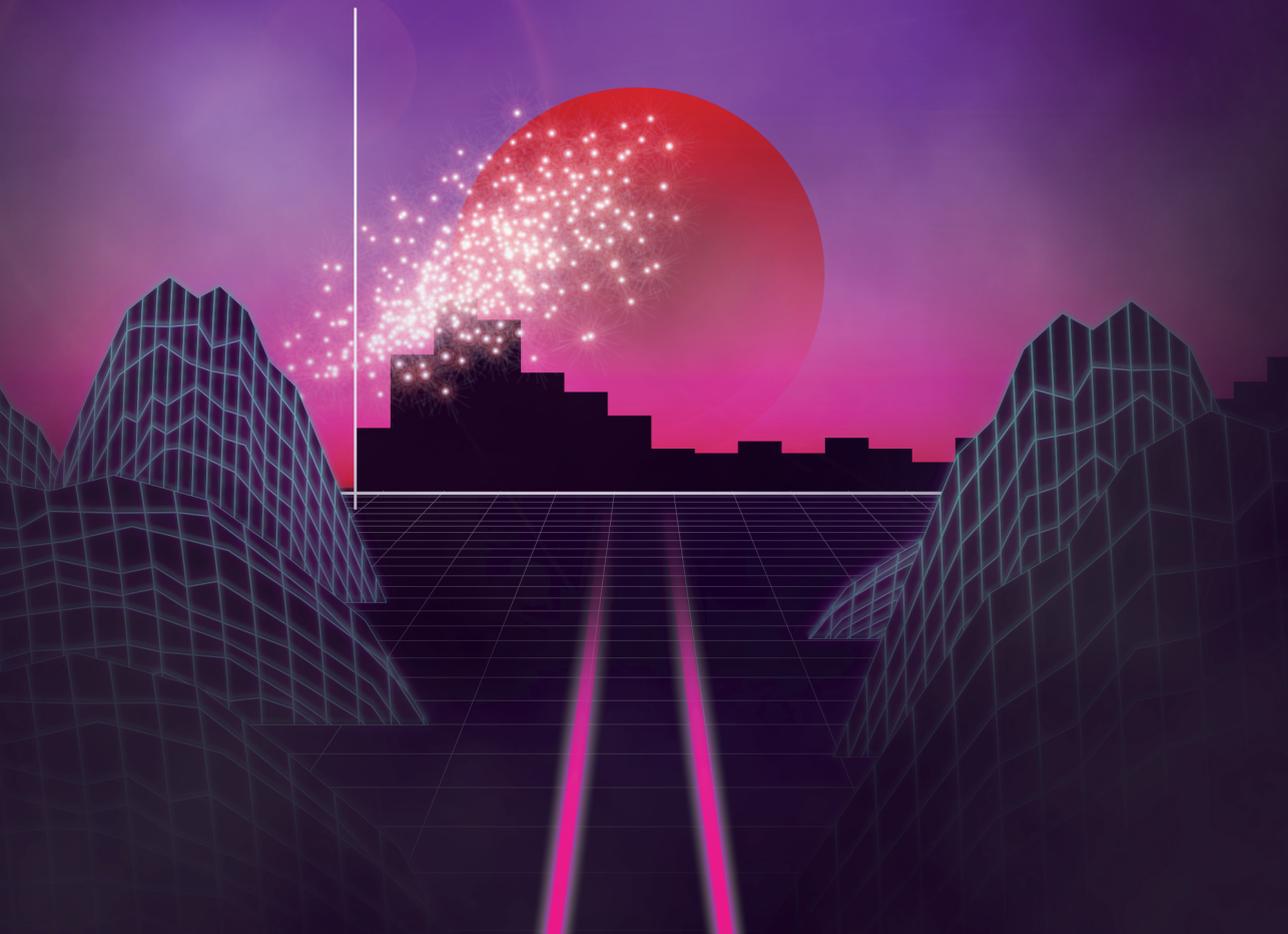


Current Challenges in Health Technology Assessment

Assessing costs and cost-effectiveness
of novel treatments in haemato-oncology

Wilhelm Frederick Thielen



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COLOFON

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Current Challenges in Health Technology Assessment

Assessing costs and cost-effectiveness of novel treatments in haemato-oncology

Uitdagingen bij het beoordelen van gezondheidstechnologieën

Het berekenen van kosten en kosteneffectiviteit van nieuwe behandelingen
in de hemato-oncologie

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
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and in accordance with the decision of the Doctorate Board.

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by

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Chapter 1

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 tisagenlecleucel 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.

PART I

Challenges in the evidence synthesis for Health Technology Assessment

Chapter 2

How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3)

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SMAA Evers, J Kleijnen

Expert Review of Pharmacoeconomics & Outcomes Research. 2016;16(6):705-721

ABSTRACT

Introduction: This article is part of the series “How to prepare a systematic review of economic evaluations (EES) for informing evidence-based healthcare decisions”, in which a five-step approach is proposed.

Areas covered: This paper focuses on the selection of relevant databases and developing a search strategy for detecting EEs, as well as on how to perform the search and how to extract relevant data from retrieved records.

Expert commentary: Thus far, little has been published on how to conduct systematic review EEs. Moreover, reliable sources of information, such as the Health Economic Evaluation Database, have ceased to publish updates. Researchers are thus left without authoritative guidance on how to conduct SR-EEs. Together with van Mastrigt et al. we seek to fill this gap.

INTRODUCTION

To support their decisions in health care, policy and decision makers need reliable information on the cost-effectiveness of health care interventions.⁵⁶ Systematic reviews of economic evaluations (SR-EEs) are a source of this information.⁵⁷ However, although these reviews have become increasingly important, little has been published on how to perform SR-EEs.⁵⁸ Without such guidance, those who wish to perform SR-EEs are left with practice guidance and recommendations that focus solely on medical efficacy research, which is usually concerned only superficially – if at all – with economic outcomes.

The vast amount of publications and their widely differing quality, together with subjective components that may guide a searcher's decision, call for standardized methods.⁵⁹ Therefore, a carefully planned strategy is essential when a thoroughly conducted SR is the goal.⁶⁰ Moreover, SRs should be reproducible, verifiable, efficient, and accountable.^{57,61,62}

With a five-step approach on how to perform SR-EEs of health-care interventions, van Mastrigt and colleagues make a first attempt to fill the gap that has occurred in the absence of both guidance and reliable and comprehensive economic databases.³⁰ Their goal is to pave the way in establishing future guidance for SR-EEs. In the meantime, their approach can be used as a preliminary manual for performing SR-EEs in a sound scientific way. Their guidance aids users in employing efficient and transparent methods, which are central to any SR.⁵⁷ Just as for part 1/3 of this paper series, this article's main target audience is developers of clinical practice guidelines (CPGs) who need a point of reference on how to perform SR-EEs. Similarly, it can be a helpful tool for researchers in health technology assessment, systematic reviewers, and for students who seek to prepare an SR-EE. To illustrate the case, we will discuss our theoretical considerations alongside a recent example of an SR-EE that was part of developing a CPG for the treatment of epilepsy in The Netherlands.⁶³

BACKGROUND

Typically, evidence for a CPG is gathered by systematically reviewing publications that are concerned with the effectiveness of different treatment options.⁶⁴ In addition, it has become increasingly acknowledged that CPGs should also entail economic evidence.^{65,66(p7),67} This can be done in two, not necessarily independent, ways: (1) an SR and critical summary of the economic evidence already published is undertaken or (2) a decision analytic model is built to model economic effects.⁵⁷ This article will focus solely on the former approach.

In general, most steps of an SR-EE involve the same stages that are needed to conduct an SR of evidence for clinical effectiveness.⁵⁷ More specifically, any SR-EE will be based on the same two-stage process that has become the established standard for SRs of effects,⁵⁷ namely: (1) developing a search strategy and (2) applying the search strategy to a set of specified

databases.⁶⁸ However, some methods of SR-EEs diverge significantly as economic outcomes replace effectiveness or safety outcomes that would be detected in SRs.⁵⁷ As a result, database selection as well as the identification of search terms and filters differs. However, guidance on how to extend a search strategy and what databases to use when seeking to incorporate EEs is scarce, fragmented, or not applicable to all cases. In this article, we will present solutions for overcoming these issues, based on published guidance in the field and our experience.

THE FIVE-STEP APPROACH FOR PREPARING AN SR-EE

Following van Mastrigt's approach for conducting SR-EEs, the first step is to compose a multidisciplinary project team, frame the study, prioritize the topics, and write and publish the protocol. With regard to the subsequent steps, it should be noted that adding a medical information specialist or librarian to the search team adds great value to the quality of the searches.⁶⁹ In the second step, EEs need to be identified; this includes (1) selecting relevant databases, (2) developing an adequate search strategy, (3) performing the searches, and (4) selecting the relevant studies. This article will provide a more detailed description of these four parts of the second step, while step 3 is described by Wijnen et al.⁷⁰ in more detail. An overview of all other steps and a detailed description of steps 1, 4, and 5 can be found in van Mastrigt et al.³⁰ For an overview of the five-step approach, see Figure 1.

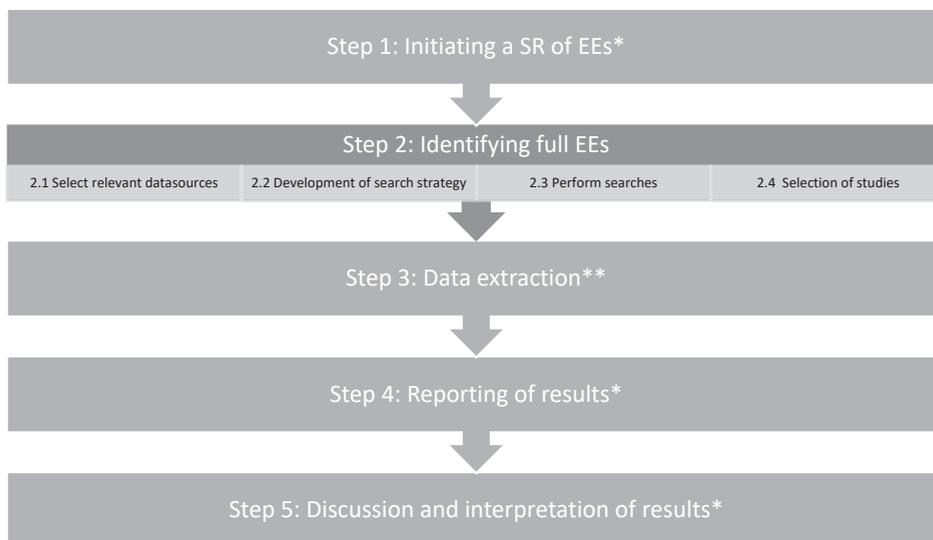


Figure 1 - An overview of the 5-step approach for preparing a systematic review of economic evaluations to inform evidence-based decisions. *Described in detail by van Mastrigt et al.,³⁰ **Described in detail by Wijnen et al.⁷⁰

STEP 2.1 OF THE OVERALL FRAMEWORK: SELECTION OF RELEVANT DATA SOURCES

Until recently, a large part of EEs in health care could be detected by searching databases that specifically focus on these evaluations, such as the U.K. National Health Service Economic Evaluation Database (NHS EED) and the Health Economic Evaluation Database (HEED). However, HEED ceased publication at the end of 2014 and is no longer accessible for searches.⁷¹ And, although still accessible through the Cochrane Library and the Centre for Reviews and Dissemination (CRD) website, the NHS EED has not been updated since March 2015.⁷²

Many databases can be accessed via different search providers and platforms, and these pose varying requirements for a search strategy. Most end users will access well-known standard biomedical databases such as MEDLINE or Embase [1]. Apart from the question of whether all EEs are indexed in these databases, records can be indexed inconsistently, and there is no uniform interpretation of the definition of EEs [3]. In addition to electronic bibliographic databases, other resources such as gray literature, research registries, or web pages may contain useful information. Also, registries of unpublished studies can be searched, and researchers can be contacted for additional data.

No database is comprehensive enough to cover all relevant published research.⁷³ Therefore, the general consensus for effectiveness is that at least several databases need to be searched for a comprehensive result.^{74–78} Guidelines for SRs recommend searching at least two bibliographic databases,^{79,80} although there is no agreed-on standard for how many should be searched.³¹ As the number of searched databases increases, database bias (referred to as the probability that the index of a record in a specific database is dependent on its results) and potential language bias can be reduced.⁸¹ Which databases should be selected for a review depends heavily on the study objectives,³¹ and there is no consensus about this either.⁸² Being aware of how each interface for searching databases works is essential, since search results might well vary if the same database is searched through different interfaces (e.g. searching MEDLINE via PubMed or via OVID).⁸²

Electronic databases for searching EEs

Backed by an extensive amount of evidence,^{83–92} Mathes et al.⁹³ recommend searching at least MEDLINE and Embase for SR-EEs. In addition, they suggest searching one health economic database, such as HEED or NHS EED. Also, the Cochrane Handbook⁹² and the manual for developing the National Institute for Health and Care Excellence (NICE) guidelines,⁶⁴ together with the Campbell and Cochrane Economics Methods Group (CCEMG),⁹⁴ emphasize the use of the NHS EED on their website when searching for economic evidence for SRs. However, as HEED is no longer available and the NHS EED is no longer updated, this advice is obsolete.

Gray literature

Gray literature (i.e. technical reports, studies, or essays that are unpublished, have restricted distribution, and are therefore rarely included in bibliographic retrieval systems)⁹⁵ has the potential to add valuable information to an SR-EE, especially when little is known about the topic under study. Although finding and including gray literature is particularly time-consuming and difficult, it is regarded as necessary for minimizing bias in reviews.⁹⁶ When possibly including gray trials, Hopewell et al.⁹⁶ recommend contacting the authors of these trials for more information. Examples of missing information could, for instance, be values for the standard deviation or variance when only the mean or median is reported.

The CRD health technology assessment database identifies gray literature.⁹⁷

Citation searching

In citation searching, the reviewers search for articles that have cited a set of relevant articles which have already been detected.³¹ For example, this can be done on the Science Citation Index Expanded™ (Thomson Reuters, United States),⁹⁸ via the Web of Science™. Citation searching can also include reference checking. Here, the reviewers can scan the reference lists of useful records previously identified to see if they refer to as yet unknown articles.

Database selection: a practical example

Wijnen et al.⁶³ sought to present an overview of published and ongoing full EEs of all health-care interventions for patients with epilepsy. The main search was conducted in March 2015. The following databases were searched: MEDLINE (via PubMed), Embase, NHS EED, EconLit, Web of Science, the Cost-Effectiveness Analysis Registry, the Cochrane Library of Systematic Reviews, the CRD Database of Abstracts of Reviews of Effects (DARE), and CRD Health Technology Assessment Database. With the first five databases, 'basic databases' were selected. Since the search was conducted up until March 2015, it can be expected that NHS EED was exhaustively searched. All other databases are classified as 'optional database' in this publication. It seems worthwhile mentioning that DARE also stopped its service in 2014.

Classification of databases

We classified several databases and websites into three categories, based on their ability to detect EEs in health care; these three categories are (1) basic, (2) specific, and (3) optional. For a complete but non-exhaustive list, see online Appendix 2A. The choice of databases is independent of whether the purpose is to conduct a multipurpose review or to develop a new CPG.

- 1) Basic databases: We refer to 'basic databases' as those that are recommended for use in any case when performing SR-EEs. Using a well-constructed search strategy, most relevant EEs will be detected.
- 2) Specific databases: For an SR on a topic for which a specific database is available, we recommend using it. Specific databases are those that provide information primarily in a particular research field. An SR on a mental health topic for instance would benefit

from searches performed on PsycINFO (American Psychological Association, United States).^{99,100}

- 3) Optional databases and websites: Under the category of ‘optional databases,’ we grouped databases and web pages that may hold additional information relevant for a more comprehensive SR. For example, optional databases will identify Health Technology Assessment (HTA) reports (Canadian Agency for Drugs and Technologies in Health [CADTH] HTA database) and conference proceedings (International Society For Pharmacoeconomics and Outcomes Research (ISPOR) website or the Cochrane Colloquium). Furthermore, trial registries may provide an outlook on what studies are currently being performed and may provide further evidence in the near future.

Until a new EE database becomes available, we recommend searching at least the basic databases MEDLINE,¹⁰¹ Embase,¹⁰² NHS EED,⁹⁷ EconLit (EBSCO),¹⁰³ and Web of Science,¹⁰⁴ bearing in mind that the NHS EED stopped updating in March 2015. If applicable, a search on a more disease-specific database can be necessary. As many optional databases should be added as is feasible.

STEP 2.2 OF THE OVERALL FRAMEWORK: DEVELOPMENT OF A SEARCH STRATEGY

Developing an entirely new comprehensive search strategy (i.e. a string of search terms) is a time-consuming effort which highly depends on the reviewer’s experience. The time needed for developing and testing such a strategy is reported to be around 20 h for experienced reviewers.¹⁰⁵ It needs to be noted that these estimates also entail the testing of such a strategy against a so-called ‘gold standard’ (i.e. a known set that entails all relevant publications).⁵⁹ However, it is not necessary to develop and test a search strategy from scratch for every new SR-EE. When designing a comprehensive search strategy, it is advised to ask the help of a biomedical information specialist, available at many universities.^{61,69,106} Considerable work has been done to support researchers in detecting relevant articles for SRs concerning the effectiveness of treatment and diagnostics. However, little has been published on empirically validated search strategies for EEs.⁵⁶ In general, a successful search strategy is regarded as one that delivers a manageable amount of references with a searcherspecified balance of sensitivity and precision.⁷⁶ The definition of what is regarded as being manageable obviously depends on the size and expertise of the review team. When making use of predefined methods for screening, researchers other than information specialists screened a median of 296 articles per hour.¹⁰⁷

Important elements in a comprehensive search strategy

In searching literature databases, a search strategy typically makes use of different search terms that are related to elements in the research question. With a so-called ‘conceptual approach’ (also known as a ‘conventional approach’¹⁰⁸), different information sources are used to identify relevant terms and their synonyms.¹⁰⁹ Several databases offer the possibility to employ medical subject headings (referred to as MeSH[®] terms in e.g. PubMed[®]), or Emtree[®] (Embase[®]). Both MeSH and Emtree groups controlled vocabulary and hence serve as thesauri used to index biomedical literature in the respective databases. For a comparison of MeSH[®] and Emtree[®], see ¹¹⁰.

Search filters are defined as a collection of search terms based on research and validated against a so-called ‘gold standard’ (i.e. a known set of relevant records),⁵⁹ used to identify certain types of records, often for very broad topics.^{59,111} They are regarded as a time-saving ‘ready-made solution’, leaving searchers ‘free to concentrate on the other aspects of the search’.⁷³ Hence, they improve both the efficiency and effectiveness of searches.⁵⁹

Although there seems to be no consensus on how to set up a good search filter, filters can be tested for their quality in terms of (1) sensitivity, (2) specificity, (3) precision, and (4) accuracy (see Table 1).⁵⁹ Sensitivity is defined as the proportion of relevant citations that were retrieved; specificity is the proportion of low-quality (or off-topic) records not detected; precision is the proportion of articles that are of high quality; accuracy is the proportion of all articles that are correctly classified.¹¹² While it should be the general aim to maximize sensitivity,⁶⁸ a high level of precision is needed to meet the requirements of guideline developers and HTA researches and to prepare scoping or rapid reviews.¹¹³ It should be noted that achieving a high degree of sensitivity is often associated with a lowering of precision and vice versa.^{58,68,113–115}

For identification of full EEs, we recommend choosing a sensitive rather than a precise filter.

Once all synonyms, MeSH/Emtree terms, and search filters are detected, they can be connected through the Boolean or proximity operators per Patient, Intervention, Comparator, Outcome (PICO) aspect. All PICO aspects are then combined with AND. Finally, the complete search strategy can be pasted into the database search interface. It needs to be noted that each interface follows specific syntax rules.¹¹⁶

Boolean operators

Search terms within a concept (synonyms) should be combined with the Boolean operator OR. Aspects and filters can be combined into a search strategy with the use of the Boolean operator ‘AND.’ In addition, some search interfaces allow the use of proximity operators such as ‘NEAR’ or ‘ADJ.’ By searching for two (groups of) words on a certain internal distance, the search achieves more specificity in comparison with combining terms with ‘AND’ and more sensitivity in comparison with searching for specific phrases. The proximity

Table 1 - Calculation of sensitivity, precision, and specificity for the evaluation of search filters.

		Manual filter (hand searching)	
		Relevant (gold standard)	Not relevant
Search filter	Retrieved	A	B
	Not retrieved	C	D
		A + C	B + D
Sensitivity:		$\frac{A}{A + C} \times 100$	
Precision:		$\frac{A}{A + B} \times 100$	
Specificity:		$\frac{D}{D + B} \times 100$	

between the words can often be set by the user. This can be of particular value if one search term can be described in several ways. The Cochrane Handbook for Systematic Reviews of Interventions (hereafter: Cochrane Handbook)⁶² recommends using the 'NEAR' operator due to its higher degree of sensitivity and precision as opposed to 'NEXT' and 'AND,' respectively. It should be noted, however, that the proximity should be used only to combine words within one aspect (such as the disease or intervention aspect). Accordingly, it cannot replace the 'AND' between aspects. Theoretically, the Boolean operator 'NOT' can be used to exclude specific aspects. It should, however, be avoided in searches for SRs or used with great caution due to the possibility that it could unintentionally remove relevant records.⁶⁸

Truncation

Most databases offer the use of truncation, which is a way to search for multiple words with the same word stem. Usually truncation is indicated with an asterisk (*) at the end of a word stem. Truncating *effectiv** would for instance search for effective, effectiveness, effectivity, etc. Likewise, some databases offer a wildcard operator (such as '?' in the Cochrane Library or '#' in Ovid), which is meant to replace one single character. Searching for *wom?n* will in this case search for women and woman.⁶⁸ Truncation should be done carefully. Truncation of the word *cost** for anything related to costs will for instance also search for costimulants which is not directly related to costs. In this example, truncation took place at a word stem that was too short.

Restrictions

Most databases allow different methods for restricting their search results. It is recommended that language restrictions not be included in the search strategy,⁶⁸ although this is not always feasible. Likewise, restrictions on dates should not be applied except for specific reasons, such as when updating earlier reviews or when a certain technique being evaluated was not present before a certain date. Formats such as letters can add relevant additional information

that relates to trial reports; they can update them or may be intended to correct mistakes. Therefore, they should not be excluded per se.⁶⁸

Selection of search terms and filters

Following the first steps of Mastrigt et al.,³⁰ the eligibility criteria for studies to be included in the SR are already defined. These criteria will inform the four basic components of the PICO scheme: population (or participant, or population), intervention, control or comparator, and outcomes;¹¹⁷ this is a helpful step in the conceptualization of the research question.⁹³ Other search tools such as PICOS (where the S refers to study design) seem to be less sensitive in comparison with PICO.¹¹⁸ Usually, not all PICO aspects are well covered by the title or abstracts or indexed key words of an article, and not all aspects are equally important.⁶⁸ Therefore, the final search strategy for SREEs will often consist of the following three main key concepts of interest: (1) health/disease, 2b) intervention, and (3) economics. Search terms for each concept can be derived from the conceptual approach or by using already existing search filters. For each concept, it is advised to include a wide range of free-text terms separated by the Boolean operator OR, to make as much use of truncation and wildcards as possible (see below),⁶⁸ and to use proximity operators if they are available in the interfaces used. Specifics of the three concepts will be discussed in the following subsection. Since February 2016, Embase provides a PICO search interface that can be useful for conceptualizing a first search strategy.¹¹⁹

Several databases offer the possibility of employing thesauri (also known as MeSH terms in MEDLINE or Emtree in Embase). These thesauri provide additional alternative terms that can be used as synonyms in the creation of the search strategy.

For English, it is recommended using both British and American spellings for the free-term search.¹²⁰

Health/disease and intervention concept

As both health/disease and intervention concepts share many features and are closely related to each other, they are discussed together. For both concepts, making use of an already existing search strategy or filters is recommended. These may be found in the appendices of Cochrane SRs, publications of the NICE,¹²¹ or other high-quality SRs. If the planned SR-EE is part of a CPG development process, information on the health- or disease-specific string can be taken from the search used to detect studies that evaluate the clinical effectiveness of the intervention of interest.

As mentioned earlier, some search filters for specific topics already exist and sometimes are even partially integrated by database providers (e.g. clinical queries in PubMed). The InterTASC Information Specialists' Sub-Group (ISSG) provides a list, updated monthly, for search filters grouped by study design and focus.¹²²

Economic concept

Search terms for the economic concept are dependent on the research question and on the type of EEs that are sought to be incorporated. If, for instance, economic modelling studies are considered for the SR, it is not enough to incorporate only economics-related search terms.

Most often, search filters and full search strategies are reported together with their respective sensitivity, specificity, precision, and accuracy. In 2009, Glanville and colleagues found that EEs cannot be identified efficiently using indexing terms provided by most databases.¹²³ Therefore, they tested the performance of available search filters for their ability to detect EEs in MEDLINE and Embase. They concluded that, while some filters are able to achieve high levels of sensitivity, precision is usually low.¹²³

Since a newly created search filter needs to be validated, its development is a challenging, time-intensive, and resource-consuming task. Some search filters for detecting EEs have been published in the literature. Although these filters have been translated to fit more than one database, the translation is not always optimal, so they are not easily transferrable between databases. The selection of an appropriate search filter depends on the scope set out for the SR, as well as on which databases are to be searched. Therefore, we refer to the regularly updated ISSG website which holds a list of published filters for finding EEs in the databases CINAHL, Embase, MEDLINE, and PsycINFO.¹²⁴ If feasible, we advise choosing a sensitive rather than a precise search filter for SRs. This is because the former will most likely detect more records than the latter.

In 2016, the CADTH issued an update to the Peer Review of Electronic Search Strategies (PRESS) guideline that aims to evaluate electronic search strategies.¹²⁵ Originally, the PRESS guideline focused on librarians and other information specialists as primary users, but it can also be of great use for researchers undertaking SRs.

Recommendations for a complete search strategy – in a nutshell

When developing the search strategy, it is important to breakdown the research question into its main conceptual elements. The PICO scheme can help with this, although not all PICO elements might be useful.

A search strategy should encompass a wide range of freetext terms, make use of proximity operators when possible, and employ thesauri. Truncation should be used with caution, and for English, British and American spelling should be used. Restrictions of search results (e.g. language and time frame) should be used as little as possible when setting up a search strategy.

Already existing and validated search filters should be selected for being highly sensitive or highly precise or a combination of both. A soundly conducted SR will profit from a sensitive rather than from a precise search filter. Filters to find EEs can be found on the ISSG website.

Developing a search strategy: a practical example

Wijnen et al.⁶³ constructed a total of eight different search strategies to cover all relevant aspects that the to-be-developed CPG should cover. To keep this example comprehensible, we will focus on the search strategy for detecting publications concerning the ketogenic diet. A schematic overview on this search strategy is depicted in Figure 2. Applying the PICO strategy to this case would detect “individuals with epilepsy” as patients, “ketogenic diet” as intervention. As no specific comparator is mentioned, it is assumed that the authors searched for any comparator possible. For this part of the CPG development process, only economic evaluations were of interest as outcomes. For studies of effects, this would obviously be different.

For the example at hand, the important aspects for a database search would thus be patient, intervention, and outcomes (since no specific comparator was of interest). For the patient and intervention aspects, an experienced information specialist compiled a broad set of search terms. For the outcome aspect, an already published search filter designed for MEDLINE was used.¹²⁶ This filter can be found on the ISSG website.¹²⁴

STEP 2.3 OF THE OVERALL FRAMEWORK: PERFORM SEARCHES

Once the search strategies for the selected databases have been created, the search can be performed. Relevant studies that are already known should be included in the newly retrieved set of articles. If not, it needs to be determined why the search strategy could not detect them. Accordingly, the search strategy might have to be adapted. This triangulation method can serve as a sort of quality check.

A clear documentation of all searches (i.e. electronic database searches and hand and reference searches) is essential for the reproducibility and future updates of the study findings.^{31,68,79,80,127} This means that the details of all searches performed (e.g. database selected, time frame covered, key words and restrictions used [i.e. the entire search strategy], number of records retrieved, etc.) should be collected systematically and added to appendices of the report (see online Appendix 2B for an example). Reference managing software (e.g. EndNote, Refworks, etc.) can be used to manage bibliographic details and deduplicate results and prepare references for publications. This will ensure efficient handling of all references retrieved from different databases.⁶⁸ The user should, however, be aware of how the reference manager used handles deduplication and the preparation of references for publication.^{128,129} Reference information for gray literature and reports can be found on WorldCat®.¹³⁰

After references from all databases have been downloaded into a reference software program, they can be deduplicated. Most reference management software programs have built-in deduplication options, but several methods have been published as well.^{131–133} Deduplication is often considered time-consuming, even when using bibliographic software, because users feel the need to check the correctness of the selected duplicates. A safe and fast method has been developed in EndNote, where fields can be set upon which the duplicates are compared.^{131,134}

The PICO scheme			
Patients	Intervention	Comparator	Outcome
Search terms for the example of Wijnen et al. ⁷⁰			
Epilepsy	AND	Ketonic diet	AND - not applicable - AND Economic evaluations
Synonyms / alternative keywords			
epilepsy[MeSH] OR epilepsy[TIAB] OR epileps*[TIAB] OR epilept*[TIAB] OR seizures[MeSH] OR seizures[TIAB] OR seizure[TIAB] OR Convulsion OR convulsions[TIAB]	"ketogenic diet"[MeSH] OR ("ketogenic"[TIAB] AND "diet"[TIAB]) OR "ketogenic diet"[TIAB] OR (ketogen*[TIAB] AND diet[TIAB]) OR "diet therapy"[MeSH] OR "diet therapy"[TIAB]		Search filter with best balance of sensitivity and specificity taken from Wilczynski et al. [51]: cost*[Title/Abstract] OR "costs and cost analysis"[MeSH:noexp] OR cost benefit analys*[Title/Abstract] OR cost-benefit analysis[MeSH Term] OR health care costs[MeSH:noexp]
<small>AND, OR = Boolean operators; MeSH = Medical Subject Heading (for MEDLINE via PubMed); TIAB = abbreviation for Title/Abstract (for MEDLINE via PubMed); * = truncation (for MEDLINE via PubMed); noexp = EXPLODE function turned off (for MEDLINE via PubMed)</small>			

Figure 2 - Schematic overview on search strategy of Wijnen et al.⁷⁰ Per PICO item, all synonyms and MeSH terms were combined with the Boolean operator OR. Truncation (in the form of an *) was used whenever possible. All search terms were restricted to be detected in title and abstracts only (see [TIAB] or [Title/Abstract]). Within one PICO item, different words can be combined with AND. For the intervention aspect, “ketogenic” was combined with “diet”. At this place a proximity operator could have been used. The same approach could also have been used for the search term “diet therapy”. To detect economic evaluations, a published search filter was copied.¹²⁶ Finally, all elements of the PICO scheme were combined with the Boolean operator AND to produce a single search strategy that could then be pasted into a MEDLINE search interface (in this case PubMed).

STEP 2.4 OF THE OVERALL FRAMEWORK: SELECTION OF STUDIES

Screening of potential relevant studies should be conducted in two stages.^{31,79} First, after removing the duplicates, all remaining records are screened, preferably by two independent reviewers,¹³⁵ on title and abstract. Studies should be selected based on the eligibility criteria stated in the published protocol (Steps 1.3 and 1.4). Second, the full-text records are screened for compliance with eligibility criteria.¹³⁵ Often it is recommended that, ideally, all steps critical for study selection (2.3 and 2.4) and for data extraction (3.1 and 3.2) should be done by two reviewers independently.^{31,80,135} However, as this is not always

achievable, one reviewer can select and extract the data, with a second one checking this for completeness and accuracy.³¹ Pilot testing of these processes should be performed using a representative sample of studies.^{31,79,135} Accordingly, the inclusion criteria should be applied to a sample of records.⁷⁹ Any discrepancies between the two reviewers should be resolved by consensus.^{31,79,135} In addition, a third reviewer may be consulted if any issues need further discussion.^{31,135} The review process can be done in different ways. As a formal measure of agreement, Cohen's Kappa can be calculated,^{31,135} although not all guidelines regard this as necessary.⁷⁹ The review process can be managed through EndNote,¹⁰⁷ but many other programs are available as well. A compendium of different tools that also calculate Cohen's Kappa automatically can be found elsewhere.¹³⁶

All information on the abovementioned processes can be reported in the study protocol and in the methods section of the publication.^{31,79,135} If there are multiple records of the same study, these records should be linked together.^{68,79,85} This can be done by making a systematic numerical order for the studies and reporting this in the results section. This could be done as follows: for the oldest report, the number '1A' (used further in SR-EE when reporting or discussing this study), '1B' for the second report of that specific study (mentioned only once in the results section when discussing the number of included studies), '1C' for the third publication, etc. A list of studies that were excluded from the SR at the full paper stage should be provided in the online appendices,^{31,135} to keep the study transparent and reproducible. This list needs to contain bibliographic details of the excluded studies and the reason for exclusion.^{31,79,135}

A flowchart of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement on study inclusion should be used to show all details of the selection process in a systematic way.^{31,79,137}

EXPERT COMMENTARY & FIVE-YEAR VIEW

As much as the development of the NHS EED and HEED databases was heralded as an improvement in providing access to EEs,¹¹³ the discontinuation of updating these databases has had a tremendous impact on how to conduct SR-EEs. The cessation of these databases created a gap, with no new database currently capable of replacing them. The scientific community seems to be reacting with procrastination. Renowned practice guidance such as the Cochrane Handbook,⁶² the NICE manual for developing NICE guidelines,⁶⁴ and other reliable sources of information (e.g. the CCEMG website⁹⁴) need to be revised and updated so that using these databases is no longer recommended. Without comprehensive economic databases, researchers need to rely on other information sources which are not specialized in EEs and must use more complex search strategies with specialized search filters to detect EE literature in available databases. Setting up a new health economic database might seem

Table 2 - Step-by-step plan on how to identify economic literature for a systematic review

Step 2: Identifying full economic evaluations	
Step 2.1 Select relevant data sources	
<i>General databases</i>	Select at least Medline, Embase, NHS EED, Econlit, and Web of Science. Be aware that NHS EED has not been updated since May 2015.
<i>Specific & optional databases</i>	Select specific databases according to your topic (if applicable). Search optional databases for HTA reports and conference proceedings.
<i>Grey literature</i>	Consider including grey literature; this can minimize bias and be a valuable source of information. Database noemen worldcat?
<i>Citation searching</i>	Search for relevant citations in already known publications. Make use of citation searching (i.e. identify articles that have cited a set of relevant articles already detected).
Step 2.2 Development of a search strategy	
<i>Search terms</i>	Make use of the PICO scheme to find relevant search terms for all important concepts/aspects of the research question. Include a wide range of free-text terms. Use proximity operators (e.g. 'NEAR', 'ADJ') if possible. Employ thesauruses and synonyms. Use truncation options for your search terms (beware not to truncate to short word stems). For English, use British and American spelling.
<i>Search filters</i>	Determine whether you want to use a more sensitive or precise search filter. SRs will profit from sensitive filters because precise filters will miss some articles. Look for search filters that filter for publication types (e.g. economic or trial publications). Choose already developed and validated filters. The ISSG website ¹²² holds a regularly updated repository of such filters.
<i>Combine search terms and filters with Boolean (AND, OR, NOT) operators</i>	Carefully consider on what basis, and if at all, you want to restrict your search results. It is not recommended that restriction be made on the basis of language or within a narrow time frame.
Step 2.3 Perform searches	
<i>Document the search process</i>	Document and report all steps of the search, including the complete search strategy for every database.
<i>Handle references</i>	Use bibliographic software to keep track of downloaded references and publications. Deduplicate the downloaded records by using a reference management software.
Step 2.4 Selection of studies	
<i>Screen references</i>	Two reviewers should screen the references independently. Screen titles and abstracts of the downloaded records based on the eligibility criteria that were set earlier.

Abbreviations: NHS EED: National Health Service Economic Evaluation Database; SRs: systematic reviews; ISSG: InterTASC Information Specialists' Sub-Group; HTA: Health Technology Assessment.

like a good solution. However, with regard to the tremendous amount of resources needed to build and maintain such information repositories, it is questionable if this will add value.

Based on several key guidelines for preparing SRs in effectiveness research and on major publications exploring methods for detecting economic publications, we issue our advice on how to identify EEs for SRs in data sources not specializing solely in health economic literature. All recommendations are compiled into a step by step plan that can be used as a checklist (see Table 2).

As yet there is no consensus on how many and which specific databases need to be searched to identify all relevant EEs. Also, there is no unanimous agreement by which methodology a solid search strategy should be developed (see for instance^{108,138}). Our contribution can thus be seen as merely temporary guidance until more methodological research on this topic has been published or new databases for EEs have been set up. With an increasing amount of validated, reliable, and user-friendly search filters to detect health economic literature, the creation of a new database specialized on health EEs might become redundant.

Updating new and existing SRs is a key objective for future research in this area,¹³⁹ particularly because many reviews are currently outdated or no longer accessible.¹⁴⁰ On the one hand, surveillance systems could assess the need for updating SRs.¹⁴¹ On the other hand, Elliott et al.¹⁴² suggest initiating living SRs which should be high quality, up-to-date online summaries of health research that are continuously updated with newly available research.

In the years to come, researchers will have the possibility to (1) implement process parallelization, (2) use novel techniques and applications to automate the process, and (3) methodologically modify certain SR processes, in order to address the issue of timeliness in the compilation of SRs.¹⁴³ Automation processes seem to be the most promising innovation in this regard,¹⁴⁴ as they would make handcrafted SRs (at least in part) obsolete.¹⁴⁵ The SR toolbox website holds a regularly updated compendium of available software tools to support the process of compiling SRs.¹³⁶ With upcoming automation processes and the increasing availability of validated search filters, it is conceivable that the cessation of health economic-specific databases will no longer be a misfortune for the scientific community. For the last decade, it seems that most research concerned with developing search strategies for detecting EEs focuses on the two major players, MEDLINE and Embase anyway.^{56,58,113,123,146,147} In the near future, a search of those two databases could possibly be sufficient to detect most EEs. However, an important step for this to become reality is that EEs must be correctly indexed. Concepts related to health economics are often broadly defined, and the mere definition of what constitutes important components of EEs differs among scholars and changes over time (see definitions of costs components in ¹⁴⁸ and ¹⁴⁹). Establishing new guidelines to stimulate a uniform use of terms could help overcome this issue.

Chapter 3

Cost of Health Care for Paediatric Patients with Sickle Cell Disease. An analysis of resource use and costs in a European country

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ABSTRACT

Background: While multiple studies have examined the cost of healthcare for one aspect of sickle cell disease care, few have focussed on the overall cost of comprehensive care for sickle cell disease.

Methods: We conducted a retrospective cohort study of children with sickle cell disease treated in a comprehensive care centre from 1 January 2015 to 31 December 2016. Healthcare utilisation of included patients was based upon data from two main sources. The clinical practice guideline was used to determine the expected resource use of routine comprehensive care (planned elective care) and the financial claims database was used to estimate real-world resource use associated with acute and inpatient care (additional care).

Results: A total of 125 children with sickle cell disease were analysed. Expenditures for these patients averaged 5,049 EUR (standard deviation [SD]: 1,634 EUR) per child per year. Total yearly costs per patient varied considerably, ranging from 669 EUR to 84,010 EUR, and less than 15% of patients were responsible for 50% of the healthcare costs. The majority (37%) of costs was associated with inpatient hospital care which increased by age group; 27% with diagnostics; 19% with treatment; 11% with outpatients' visits and 6% with emergency care.

Conclusion: We have described real-world resource use and expenditures for children with sickle cell disease in a European comprehensive care centre. It seems that costs of a comprehensive approach with effective management in the outpatient setting is favourable when compared to episodic healthcare.

INTRODUCTION

Sickle cell disease

Sickle cell disease is an autosomal, recessively inherited haemoglobinopathy characterised by chronic haemolytic anaemia, painful vaso-occlusive crises and progressive organ failure leading to decreased life expectancy. It is the most common monogenetic disease worldwide with an estimated 350,000 births annually and an important public health problem according to the World Health Organisation (WHO).¹⁵⁰

Ninety percent of the global burden of sickle cell disease occurs in sub-Saharan Africa, where the majority of children with the disease do not live beyond five years of age.^{150,151} In contrast, life expectancy in well-resourced countries has significantly improved with almost all infants surviving into adulthood.¹⁵² Nevertheless, in these countries, life expectancy of patients with sickle cell disease is still 20 years shorter than the average life span of healthy adults.¹⁵³

In the Netherlands, approximately 1,500 individuals currently have sickle cell disease, of which half are children and the carrier incidence is 0.4%.^{154,155} Most of those affected are from Surinam, Asian or African ancestry, with a minority being of Afro- Caribbean or Middle Eastern descent.¹⁵⁶ More than a quarter of Dutch patients are treated in one of the largest comprehensive sickle cell centres in the Netherlands; the Erasmus University Medical Center – Sophia Children’s Hospital (Erasmus MC). To ensure consistency in comprehensive care and reduce levels of morbidity and mortality,¹⁵⁷ all children with sickle cell disease in the Netherlands are treated according to the national ‘Clinical Practice Guideline for Paediatric Sickle Cell Disease’ (CPG; Table 1).¹⁵⁸

Cost of healthcare

Generally, sickle cell disease together with its related comorbidities and complications results in high utilisation of medical resources such as emergency room visits and hospitalisation.^{159–161} Knowledge of expenditures associated with sickle cell disease can be used to serve as an incentive for further improvement of prevention and management strategies for disease symptoms and complications, resulting in both better care and reduced costs. In addition, estimating cost of care is important as it may ensure appropriate allocation of resources and reimbursement tariffs. However, most cost-of care studies have focussed on only one or two aspects of care, such as hospitalisations and physician visits,^{162–165,166(p)} and few studies have examined healthcare expenditures exclusively for children. Moreover, the majority of studies are based on data from Northern America,^{161,167–170} and due to large differences in healthcare systems, economic evidence of costs might not be generalizable to European countries.

Table 1 – Summary of the clinical standard treatment guideline for paediatric sickle cell disease in the Netherlands

Items	Frequency			
	Birth-12 mths	12 mths-5 yrs	5-1,3 yrs	13-19 yrs
Laboratory analyses				
- Complete blood count	3x	4x	4x	6x
- Red blood cell indices	3x	4x	4x	6x
- Low Density Lipoprotein	2x	4x	4x	6x
- Bilirubin	2x	4x	4x	6x
- Liver and renal panel	2x	4x	4x	6x
- Iron status	NA	4x	4x	6x
- Folic acid and cobalamin	NA	4x	4x	6x
Haemoglobinopathy specific analyses				
- Haemoglobin phenotyping	2x	1x	NA	NA
- Haemoglobin genotyping	1x	NA	NA	NA
- Alpha thalassemia genetic mutations panel	1x	NA	NA	NA
- Glucose-6-phosphate dehydrogenase enzyme deficiency testing	1x	NA	NA	NA
Clinical geneticist outpatient visit	1x	NA	NA	1x
Paediatric haematologist outpatient visit	4x	8x	16x	12x
Urine analyses:	NA	NA	8x	6x
- Dipstick				
- Sediment				
- Protein-creatinine ratio				
Transcranial Doppler	NA	4x	13x	6x
Chest X-ray	NA	NA	NA	1x
Electrocardiography	NA	NA	NA	1x
Abdominal ultrasound	NA	NA	NA	1x
Echocardiography	NA	NA	2x	1x
Ophthalmic screening	NA	NA	NA	4x

Abbreviations: mths, months; NA, not applicable; yrs, years.

Study aims

Primary aims of this study were to (a) investigate overall cost of healthcare resource use for paediatric patients with sickle cell disease in a European country and to (b) identify major cost drivers.

METHODS

We retrospectively estimated healthcare costs of a paediatric cohort with sickle cell disease at the Erasmus MC by quantifying and valuing resource use for a period of 24 months.

Study population

All children with sickle cell disease visiting the Erasmus MC for routine or emergency care in 2017 were included in the study cohort. Individual patient-level data was retrospectively analysed from the period 1 January 2015 to 31 December 2016 (i.e. 24 months). Patients were categorised into four age groups; (A) < 1 year, (B) ≥1-5 years, (C) ≥5-13 years and (D) ≥13-19 years to reflect the categorisation of age used in the CPG. Unless patients were born during the observation period, they all contributed 24 months of follow-up time. To account for a shorter follow-up time of new-born patients and a possible switch between age groups during follow-up, we calculated the weighted average of all costs. Weights were based on the patient-months-at-risk during the retrospective study period (i.e. 24 months).

Resource use

Resource use per patient was quantified for five main resource use categories, based on two main data sources.

The two main sources of data included the national CPG, and the Erasmus MC financial claims database. The five resource use categories included: diagnostics, emergency room visits, inpatient care, outpatient care, and treatment.

The CPG was used to determine the *expected resource use* of routine comprehensive care (planned elective care) for the categories of diagnostics, outpatient visits and inpatient visits. This implied that every child with sickle cell disease follows recommendations for health maintenance and monitoring of disease-modifying therapy and therefore also uses all resources and generates all costs. Consequently, a full compliance to CPG was assumed. In addition to the resource use stated in the CPG, the Erasmus MC employs a specialised paediatric nurse practitioner (0.8 full-time equivalent) for both inpatient and outpatient care coordination of children with sickle cell disease. We assumed 45 minutes of working time for the nurse practitioner per planned outpatient visit for elective care (i.e. CPG). Remaining costs were distributed over all non-elective outpatient (90%) and inpatient visits (10%) as obtained from the financial claims database.

The Erasmus MC financial claims database was used to estimate real-world resource use associated with acute and inpatient care for all five resource use categories. This database contained all recorded hospital procedures and visits to the Erasmus MC and all inpatient visits at local hospitals. For the latter we had no access to detailed information about the inpatient episodes. Recorded resource use from the Erasmus MC financial claims database that exceeded the expected resource use in frequency, was regarded as resource use *additional*

to CPG. For instance, children below one year of age were expected to have five (routine) outpatient visits per year. In case a child in this age group had eight recorded outpatient visits in one year, only three were regarded as *additional* visits to the CPG.

The included items for the CPG and financial claims database per resource use category are summarised in Table 2.

Table 2 – Resource use categories and included items per data source

Resource use category	Items CPG	Items financial claims database
Diagnostics	Diagnostic procedures (including laboratory and diagnostic imaging)	Additional diagnostic procedures (i.e. X-rays, abdominal ultrasound)
Treatment	Standard medication and vaccinations	Additionally prescribed medication, surgery and blood transfusions
Emergency care	NA	Emergency room visits
Outpatient care	Routine visits to the outpatient clinic and care by specialized paediatric nurse practitioner	Additional visits to the outpatient clinic or medical social work and additional care by specialized paediatric nurse practitioner
Inpatient care	NA	Inpatient visits (including ICU) and day patient visits

Abbreviations: CPG, clinical practice guideline; ICU, intensive care unit; NA, not applicable.

Resource valuation

Prices for the resource use category ‘diagnostics’ were based on tariffs published by the Dutch Healthcare Authority (NZa) in 2019.¹⁷¹ Since prices for haemoglobin phenotyping and haemoglobin genotyping were not available from this source, they were based on local, internal prices. Medication prices were acquired from the Dutch Healthcare Insurance Board.¹⁷² Prices for surgical procedures (e.g. cholecystectomy) were based on prices published in 2017 by NZa.¹⁷³ Costs for both outpatient and inpatient visits were calculated in accordance with the Dutch costing manual.¹⁷⁴ The salary for a specialised paediatric nurse practitioner was taken from the Dutch collective labour agreement for hospitals (CAO).¹⁷⁵

Prices for the resource categories of emergency room visits, outpatient care and inpatient care are summarised in Table 3.

Where relevant, prices were indexed to 2019 euros using the pertinent consumer price index (CPI) published by Statistics Netherlands (CBS).¹⁷⁶ All statistical analyses were performed in R (version 3.6.1) using R Studio (version 1.2.1335) (supplement A for loaded R packages). All variables were analysed using descriptive statistics. Categorical variables are presented in percentages and (total) numbers. Continuous variables such as resource use frequencies and costs are summarised by weighted means and standard deviations. Summary statistics are presented in an aggregated way (i.e. across all resource use categories) for the overall cohort. Weighted mean costs are presented per age group and resource use category.

Table 3 - Prices of emergency room visits, outpatient and inpatient care

Resource use category ^a	Item	Average yearly resource use frequency, per age group based on CPG	Price in 2019 (EUR)	Source
Emergency room visits	Emergency room visit	NA	277	Dutch costing manual ²⁵
Inpatient care	Inpatient day at academic hospital	NA	669	Dutch costing manual ²⁵
	Intensive care unit (ICU) visit	NA	2309	Dutch costing manual ²⁵
	Inpatient day at local hospital	NA	473	Dutch costing manual ²⁵
	Day patient visit	NA	319	Dutch costing manual ²⁵
Outpatient care	Outpatient clinic visit (paediatric haematology clinic)	A: 5 B: 2.5 C: 1.5 D: 1.5	108	Dutch costing manual ²⁵
	Medical social work visit	NA	69	Dutch costing manual ²⁵
	Specialised paediatric nurse practitioner visit (per 45 minutes)	A: 5 B: 2.5 C: 1.5 D: 1.5	25	Dutch collective labour agreement for hospitals ²⁶

Abbreviations: CPG, clinical practice guideline; ICU, intensive care unit.

^aAll care took place at the ErasmusMC- Sophia Children's Hospital, except for inpatient days at a local hospital.

RESULTS

A total of 125 patients were retrospectively analysed based on the Erasmus MC financial claim database. The mean age was 7.9 years (SD: 4.7 years) on 31 December 2015 (first year of observation) and 8.6 year (SD: 4.9 years) on 31 December 2016. Forty-three percent were female patients, five patients entered the cohort as new-borns in 2015 and 2016. Summary statistics for patient's age, sex, haemoglobin genotype at the end of the observations period (31 December 2016) are shown in Table 4 (see online Appendix 3B for additional information on the distribution of genotypes across age groups).

Overall, 52 of 125 patients (43%) had inpatient care during the study period. These patients had a total of 133 admissions with an average length of stay of 5.2 days (SD: 4.6). On average, children were seen on an outpatient basis 2.1 times per year and admitted as inpatients 3.1 times per year. Patients in age groups A and B had no additional outpatient visits to the planned visits according to the CPG. For age groups C and D, the average yearly additional outpatient visits were marginal. The number of patients per age group, their mean years at risk and summary statistics for inpatient and outpatient visits are presented in Table 5.

Table 4 – Patient characteristics

Variable	Entire retrospective cohort (values on 31 December 2016)
Patients (n)	125
Mean age (SD)	8.6 (4.9)
Gender, n (%)	
Female	53 (42)
Male	72 (58)
Haemoglobin genotype, n (%)	
HbSS	76 (60.8)
HbSC	31 (24.8)
HbS β^+ thalassemia	8 (6.4)
HbS β^0 thalassemia	4 (3.2)
Other (i.e. HbSdelta β^0 , HbArab β^0)	6 (4.8)

All patients (n = 125), accrued total cumulative costs of 1,205,919 EUR during the 2 years observed. For patients with a full follow-up time (i.e. 24 months), yearly total costs per patient varied considerably, ranging from 669 EUR to 84,010 EUR. Of the total expenditures for all patients, approximately 50% of the costs were induced by 18 children (i.e. 14% of the total patient population) and approximately 80% of the costs were induced by 65 children (i.e. 52% of all patients). The distribution of HbSS and HbSC genotypes in the 18 children inducing 50% of the total costs was 83.3% and 11.1%, respectively.

Average yearly expenditures for all 125 children were 5,049 EUR (SD: 1,634 EUR). The majority (37%) of costs was associated with inpatient care; 27% with diagnostics; 19% with treatment; 11% with outpatient care and 6% with emergency room visits. The average

Table 5 - Outpatient and inpatient visits per person year

Age group	Patients (n)	Mean years at risk (y)	Total number of outpatient visits (n)	Mean outpatient visits per person per year (n)	Total number of inpatient care days (n)	Mean inpatient days per person per year (n)	Total number of emergency room visits (n)	Mean emergency room visits per person per year (n)
Total ^a	125	1.9	496	2.1	749	3.1	253	1.1
A	17	0.5	47	5.0	10	1.1	32	3.4
B	49	1.4	168	2.5	122	1.8	90	1.3
C	69	1.7	194	1.7	302	2.6	67	0.6
D	29	1.6	87	1.8	315	6.6	64	1.3

^aThe sum of patients in each age group is not equal to the total number of patients studied, since children were analysed in older age groups when applicable during the 24-month observation period. The mean number of visits was calculated by dividing the total number of visits (per stratum) by the total years at risk (not the total number of patients), as some patients did not contribute an entire 2 years to each age group (due to increasing age and switching between categories).

yearly costs per patient and age group are depicted in Figure 1. Again, average costs vary considerably between age groups, which is mainly related to differences in the number of inpatient days. Major cost drivers for age group A and B were diagnostics and treatment, respectively. For age groups C and D, the major cost drivers were inpatient care, although for age group C, the average difference in costs between diagnostics (1,355 EUR) and inpatient care (1,488 EUR) could be regarded as marginal. Average yearly costs for inpatient care were higher in older age groups and nearly three times as high in age group D compared to group C. Only for age groups C and D, we observed stays at the intensive care unit (resource use category inpatient care) with a slight increase from age group C to D. More information on the distribution of inpatient care across age groups can be found in online Appendix 3C.

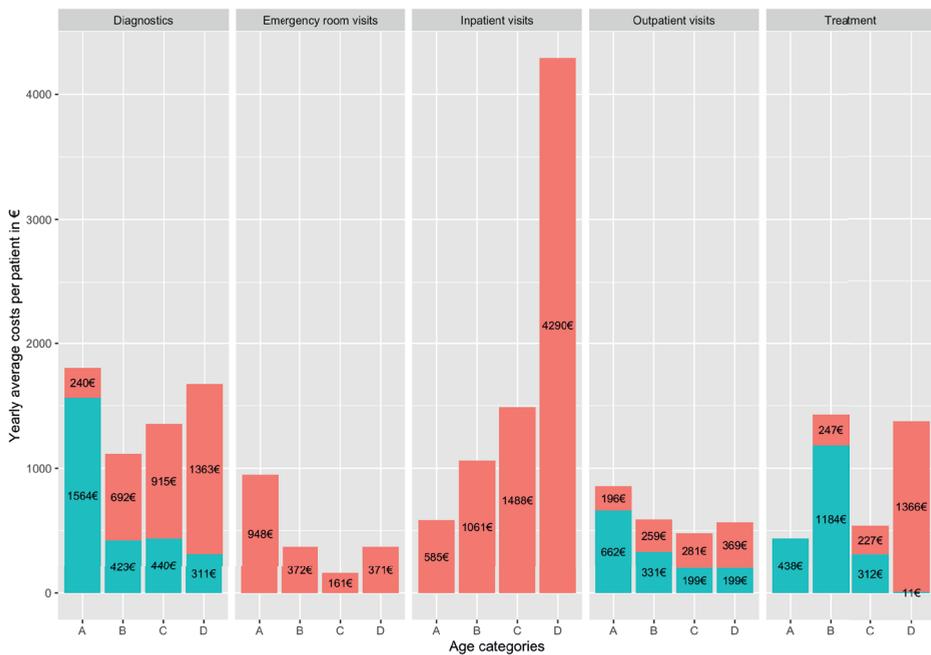


Figure 1 - The average yearly costs per patient and age group. Green: Yearly mean costs according to the clinical practice guideline. Red: Yearly additional mean costs based on the Erasmus Medical Center financial claims database.

DISCUSSION

Healthcare utilisation and expenditures

Although healthcare utilisation and costs among children with sickle cell disease have been studied previously,^{161,167-170} studies from European comprehensive care centres are scarce and have only focussed on one aspect of care such as hospitalisations costs.^{163,177} To our

knowledge, this is the first study describing costs from a European comprehensive care centre combining standard treatment costs with real-world resource use.

The total yearly costs of healthcare for children with sickle cell disease, including inpatient care, outpatient care, diagnostics and treatment averaged 5,049 EUR (SD: 1,634 EUR) per patient per year. This is much lower when compared to cost of healthcare for paediatric patients with sickle cell disease in other studies. Kauf et al. calculated total costs of healthcare for children with sickle cell disease aged 0-9 years to be 10,704 USD (8,906 EUR) (SD: 24,696 USD [20,548 EUR]) per year, of which more than 75% were associated with inpatient care.¹⁶¹ In our study, inpatient care accounts for a much smaller proportion of total costs (i.e. 37%). As a consequence, this substantially reduces healthcare costs as inpatient care is generally more expensive compared to comprehensive healthcare at specialised outpatient clinics. The study of Pizzo et al. is up until now the only cost of care study in sickle cell disease performed in Europe.¹⁶³ They retrospectively assessed the cost of inpatient care for vaso-occlusive crises in the United Kingdom between 2010 and 2011. For children aged 1-9 years they reported mean admission costs to be 1,732 GBP (2,379 EUR). Their analysis underestimates the real costs of inpatient care, as it only considers the cases with crises as a primary diagnosis.¹⁶³ In our study, average yearly inpatient costs for children aged 1-5 (age group B) and 5-13 (age group C) years old was respectively 1,061 EUR and 1,488 EUR. However, care should be given to comparing costs, as factors such as healthcare financing, social and political structures as well as types of treatment regimen can vary greatly among different countries. For example, due to differences in expert opinion, the most recent guideline of the National Heart, Lung and Blood Institute advises transcranial Doppler screening every year, compared to twice a year in the Dutch CPG. Furthermore, most cost-of-care studies use the terms cost, charge and fees synonymously or confuse reimbursement with costs, making it even harder to compare international data.¹⁷⁸

Sickle cell disease varies greatly in severity, with some children relatively asymptomatic while others are severely ill. As a consequence, substantial variation in healthcare costs is observed among children with sickle cell disease.^{162,167,168,170} We also observed this variation; a relatively small fraction of patients accounted for half of the total costs (i.e. 18 children generating approximately 50% of the costs). Although our study did not collect data on clinical heterogeneity (e.g. organ damage), these 18 patients are most likely patients with more severe symptoms. Furthermore, the majority of these 18 patients had HbSS sickle cell disease, which is often associated with a more severe phenotype. To establish and quantify the effect of disease severity on healthcare costs, further studies with larger samples sizes and longer follow-up periods need to be conducted.

Although the clinical features of sickle cell disease are heterogeneous, and therefore also the associated costs both within and across age groups, yearly additional mean costs based on the financial claims database seemed to increase with age for all resource use categories. This is consistent with previous research showing that age is an important determinant of disease

severity, since older patients are more likely to accumulate organ damage and dysfunction and have more frequent painful vaso-occlusive crises.^{179–183} However, yearly additional mean costs for emergency room visits follow a reverse trend (i.e. decrease between age groups A to C), while they increase for age group D again. A similar pattern is seen in the general paediatric population, in which young children also constitute a disproportionately high share of paediatric emergency care, mostly due to respiratory infections.^{184,185} In addition, parents tend to be more anxious when their child has just been diagnosed with sickle cell disease (via the newborn screening program), possibly leading to more frequent hospital visits.

Estimating cost of care is important for appropriate allocation of resources and reimbursement tariffs. Furthermore, specific to the healthcare system in the Netherlands, knowledge of healthcare utilisation and expenditures for patients with sickle cell disease may help to establish a diagnosis treatment combination (DBC) for (paediatric) patients with sickle cell disease. DBCs describe a complete care episode and are used as the basis for remuneration negotiations between hospitals and health care insurers. Currently, haemoglobinopathies (including sickle cell disease and thalassemia) do not have a separate DBC code and are declared by the DBC ‘anaemia not otherwise specified’. We hope this study will play a role in the authorisation of a DBC for paediatric sickle cell disease, by giving insight into overall cost of healthcare resource use for sickle cell disease patient in the Netherlands.

Limitations

This study is not without limitations which need to be considered when interpreting the results. Firstly, it is important to note that our analyses do not aim at deriving statistical inference and therefore our results are descriptive in nature. Secondly, sample size (125 patients), information about patient characteristics, and follow-up time (24 months) were limited. A further stratification into subgroups according to potential cost predictors was therefore not possible. Thirdly, a substantial proportion of patients were admitted to local hospitals. There are more than ten local shared care centres, all with their own medical databases, which are not linked to the financial claims database of the Erasmus MC. Although inpatient days were manually retrieved, detailed information about those care episodes, especially with regard to treatment and diagnostics, is missing. Hence, the estimated total costs reported for these items should be seen as lower limits of the actual costs. For example, although most complex care will have been given at the Erasmus MC, some children may have had a blood transfusion or imaging procedures during admissions at a local hospital. These interventions remain unknown and are therefore not reflected in the total costs. Nevertheless, by including the major cost driver (inpatient days in local hospital) we believe that results will not be substantially different. The Sickle Cell Outcome REsearch (SCORE) consortium of the Netherlands is currently developing a multicentre database for (paediatric) sickle cell patients, which is an important step towards more detailed analysis of patient-related data. Fourthly, none of the patients in our cohort had a haematopoietic stem cell transplantation

(HSCT) during the observed time period. Although HSCT is still a relatively uncommon treatment, median total costs for children with sickle cell disease is around 413,000 USD (343,627 EUR) for inpatient care and 18,000 USD (14,977 EUR) for outpatient care,¹⁸⁶ which would consequently have increased total annual costs when performed. Finally, it is important to note that we have adopted a health care perspective approach, meaning that patients costs (i.e. patient's time lost from school, transportation costs and parental loss of wage-earning capacity due to caretaking of a chronically sick child) were not accounted for in calculations. Further research is warranted to determine this important cost component.

CONCLUSION

In summary, we have described a detailed investigation of resource use and cost of healthcare for paediatric patients with sickle cell disease in the Netherlands over a 2-year period, retrospectively. Sickle cell disease is a chronic, complex and often unpredictable disease requiring life-long management. Our analyses suggest that costs of a comprehensive, multidisciplinary approach with effective management in the outpatient setting, is favourable when compared to episodic healthcare. Lower resource use and costs were observed for acute care and inpatient facilities. However, care should be given with regard to comparing our data to other countries. Further studies including more patients with longer follow-up times are needed to confirm our findings. In addition, to enhance medical outcomes and decrease healthcare utilization and costs, further investigation of the small subset of children who consume a large percentage of the resources is required.

Chapter 4

Second-line treatment for acute graft-versus-host disease with mesenchymal stromal cells: A decision model

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ABSTRACT

Objective: No standard second-line treatment exists for acute graft-versus-host disease steroid-refractory (SR-aGvHD), and long-term outcomes remain poor. Mesenchymal stromal cells (MSCs) have been evaluated as treatment, but no disease model (DM) exists that integrates and extrapolates currently available evidence. The aim of this study was to develop such a DM to describe the natural history of SRaGvHD and to predict long-term outcomes.

Method: The DM was developed in collaboration with experts in haematology-oncology. Subsequently, a model simulation was run. Input parameters for transition and survival estimates were informed by published data of clinical trials on MSC treatment for SR-aGvHD. Parametric distributions were used to estimate long-term survival rates after MSCs.

Results: The newly developed DM is a cohort model that consists of eight health states. For the model simulation, we obtained data on 327 patients from 14 published phase II trials. Due to limited evidence, DM structure was simplified and several assumptions had to be made. Median overall survival was 3.2 years for complete response and 0.5 years for no complete response. **Conclusion:** The DM provides a comprehensive overview on the second-line treatment pathway for aGvHD and enables long-term predictions that can be used to perform a cost-effectiveness analysis comparing any treatment for SR-aGvHD.

INTRODUCTION

Despite decades of research, acute graft-versus-host disease (aGvHD) is still one of the leading causes of death after haematopoietic allogeneic stem cell transplantation (HSCT) for both paediatric and adult patients.^{187,188} Immunosuppressive therapy with systemic corticosteroids is the first-line treatment option. However, latest available studies estimate that about 50%-70% of the patients do not respond to this therapy.¹⁸⁹⁻¹⁹¹ Currently, there is no standard second-line treatment available and outcomes in terms of morbidity and mortality remain poor.¹⁹¹⁻¹⁹⁵

Since 2004, mesenchymal stromal cells (MSCs) are increasingly studied in phase II clinical trials as a therapeutic option, demonstrating positive treatment effects for steroid-refractory (SR)-aGvHD.^{196,197} However, most of these trials are single-arm studies or case studies or include a limited amount of patients (<50 participants), making reliable and meaningful conclusions challenging. Ideally, the effectiveness of MSC should be tested through phase III randomised controlled trials (RCTs), but these trials are difficult to perform due to regulatory and patient population-related issues.¹⁹⁷⁻¹⁹⁹ In 2010, results of one RCT (Prochymal; Osiris Therapeutics, Inc. Columbia, Maryland, United States) were released in the form of an unreviewed abstract.²⁰⁰ Further, a multicentre RCT is currently being conducted by the European Union Horizon 2020-funded research consortium RETHRIM (REgeneration THRough IMmunomodulation)²⁰¹ (i.e. the HOVON 113 MSC trial²⁰²). The latter study aims to determine the efficacy and cost-effectiveness of MSC as part of a second-line treatment for aGvHD.

In the absence of reliable and conclusive RCT data, several options exist to aggregate and synthesise currently available evidence of MSCs as a treatment option for SR-aGvHD. These include metaanalyses, observational databases, the aggregation of expert opinion or decision analytic modelling.²⁰³ Thus far, four reviews that include currently available trials testing MSC as treatment for SR-aGvHD have been published,^{197-199,204} of which two are meta-analyses.^{197,204} However, none of the reviews combine available patient-level data (PLD) of the phase II trials to predict and model long-term outcomes of MSC treatment.

The aim of this study was to develop a disease model (DM) to describe the natural history of SR-aGvHD progression and its treatment pathways. The DM can be used to predict long-term outcomes and cost-effectiveness of current (eg, MSC treatment) and future treatment options for SR-aGvHD. To test the practicability of the model, we aimed to gather and implement PLD of a second-line treatment option. Ultimately, our model may facilitate clinical decision-making under conditions of uncertainty.²⁰⁵⁻²⁰⁷ When costs are added, this model can be a valuable tool for reimbursement decision-makers.¹⁹

METHODS

Part 1: designing and structuring the model

Model characteristics

The aim of the DM was 2-fold. First, it needed to represent the natural history of SR-aGvHD and its treatment pathways in a simplified manner. Therefore, the DM focusses on the SR-aGvHD only until patients either progress, relapse, develop chronic GvHD or die. Second, it needed to be easily adaptable to a cost-effectiveness model at a later stage. Therefore, the DM was built based on clinical expertise, previously published literature^{189,191,196,208,209} and the R ETHRIM protocol.²⁰¹ According to the ISPOR recommendations for good modelling practice,²¹⁰ we consulted clinical experts to ascertain that the model represents the disease process and addresses the decision problem of determining which one second-line treatment option is (cost-)effective when compared to another therapy option. We employed a convenience sample to include the clinical experts from the R ETHRIM consortium. To be part of R ETHRIM, consortium members needed to prove extensive research and treatment experience in the field of HSCT and work at a HSCT specialised treatment centre. All experts involved in this research thus have various professional backgrounds (e.g., internal medicine, haematology, oncology or transfusion medicine) and originate from five EU member states (Germany, Italy, The Netherlands, Spain and Sweden). A European perspective on the disease and treatment pathway(s) of SR-aGvHD was hence ensured.

Involvement of experts

Experts were consulted via email, during several telephone conferences and consortium meetings. This process was iterative until a final model version was regarded to fully represent the natural disease and treatment pathway. In addition to the several consultations, the experts were asked to give written feedback on an earlier model version by means of a semistructured questionnaire. Choosing the appropriate model type (eg, decision tree, Markov process) was also based on the ISPOR recommendations for good modelling practice.²¹⁰

Part 2: model simulation

Model input parameters

As MSCs are widely studied in numerous phase II clinical trials and case studies since 2004,^{196,199} we selected this treatment option to perform a model simulation. For the model input parameters, we identified relevant studies testing MSCs for the treatment of SR-aGvHD from the recent reviews of Chen et al.,²⁰⁴ Munneke et al.,¹⁹⁸ and Hashmi et al.¹⁹⁷ Additional PLD were obtained for studies whose principal investigator was a member of the R ETHRIM consortium.

Data were extracted using a prespecified extraction form aiming at capturing all available data that describe the disease and treatment pathway (see online Appendix 4A). The clinical effectiveness of MSC treatment was obtained from PLD of the reported first response evaluation or reconstructed from the published Kaplan-Meier curves. Studies not reporting these data were excluded.

To extrapolate the survival data beyond the observed time horizon, we followed the 2013 updated NICE Decision Support Unit recommendations.²¹¹ Accordingly, considered parametric survival models for the DM included exponential, Weibull, Gompertz, loglogistic, lognormal and generalised gamma distributions. Parametric models were evaluated through visual inspection, Akaike's information criterion (AIC) and Bayesian information criterion (BIC) tests as well as clinical validity according to the expert group.

Simulation

We ran a base-case simulation with a hypothetical patient cohort comprising 100 patients with aGvHD grades II-IV. Survival was modelled on a lifetime horizon, whereas it was assumed that patients do not exceed the age of 99 years.²¹² Health outcomes of the simulation were expressed in life-years (LYs). As future health effects are valued lower than immediate effects,¹⁹ we adjusted future health outcomes (LYs) to "present values" according to the Dutch guideline for economic evaluations in health care.^{213,214}

All statistical analyses were conducted in RStudio (version 1.0.143, R version 3.4.1). Comprehensive R Archive Network (CRAN) packages used included survival, flexsurv, survminer and plyr.

RESULTS

Part 1: designing and structuring the model

Model characteristics

We opted for a cohort-based Markov model, which represents the most relevant responses and outcomes to second-line treatment for aGvHD in corresponding health states. A Markov model consists of mutually exclusive health states that are associated with different outcomes and costs and provides an efficient structure to simulate a group of patients over time. Patients can change from one health state to another (ie, transit) at specified time interval (ie, cycles). Outcomes and costs are calculated for the entire time horizon of the model, taking into account the distribution of patients amongst the states at each cycle.^{215,216} Outcomes may entail clinical effectiveness outcomes (eg, response to treatment) as well as health-related quality of life (HRQoL) measures.

The DM comprises eight health states: (a) treatment for SRaGvHD II-IV, (b) response to treatment (complete or partial response), (c) sustained response, (d) treatment failure (stable or progressive disease), (e) relapse/persistent aGvHD, (f) third-line aGvHD therapy, (g) relapse or adverse events of haematologic disease requiring reinitiation or intensification of immunosuppression and (h) death (see Figure 1 for the model diagram). These states were primarily based on the HOVON113 MSC treatment protocol and expert opinion (see section “Involvement of experts”). Four response categories are defined: complete response (CR) is defined as the absence of all sign and symptoms of aGvHD; partial response (PR) is the improvement of aGvHD by at least one grade; stable disease (SD) is no change in aGvHD; and progressive disease (PD) is the worsening of aGvHD by at least one grade. The cycle duration was set at 28 days according to the recommendation by Martin and colleagues on the standardised time period to evaluate aGvHD response.²¹⁷ In addition, we applied a half-cycle correction for the calculation of the model outcomes.

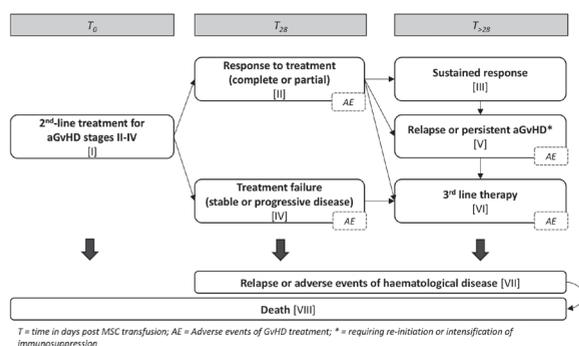


Figure 1 – Design of the decision model for MSC treatment in aGvHD

The model starts with treatment for SR-aGvHD (a) at time 0 (T0). Within 28 days after treatment (T28), patients either respond [ie, transit to the response to treatment health state (b)] or have a treatment failure (d) or die (h). Responders (b) can have a sustained response (c), relapse or have a persistent aGvHD grade that requires the reinitiation or intensification of immunosuppression (e), or enter third-line therapy (f).

Patients with a treatment failure to the initial MSC treatment (d) will directly receive third-line treatment (f). Adverse events (AEs) of treatment are not defined as a separate health state, but are possible within health states (b), and (d)-(f). At any time and from any health state, patients can transit to relapse or experience of an adverse event of the underlying haematological disease (g), or death (h). Death is an absorbing health state, meaning that once entered, patients remain in this health state.

In the model, all health states are defined as mutually exclusive although in clinical practice patients may sometimes fit the criteria of multiple health states. In these cases, patients are assigned to the health state with the largest impact on outcomes and costs. For example,

patients with treatment failure [health state (d)] may experience a relapse of the disease [health state (g)]. These patients are assigned to the relapse health state (g) although they also fit the criteria for treatment failure. The increasing numbering of the model states indicates the expected increasing impact on both outcomes and costs, according to expert opinion.

Involvement of experts

The team of clinical experts consisted of eleven members from five different countries (Germany, Italy, the Netherlands, Spain and Sweden). A preliminary model based on the HOVON113 MSC treatment protocol was presented to all consortium members at the third RETHRIM consortium meeting. Because the structure of the model was deemed incomplete, alternative treatment pathways and additional health states were discussed in detail. This led to a refinement of the existing model states and to the addition of the following health states: relapse or adverse events of haematological disease, and adverse events. The new version of the model was then presented and discussed at the fourth RETHRIM consortium meeting. To allow for written feedback, experts were asked to fill out a semistructured questionnaire at the fifth consortium meeting. Subsequently, the model was amended and a final version was approved by all experts.

Part 2: Model simulation

Model input parameters

We detected 18 studies that reported on phase II trials and collection of case studies,^{190,218–234} of which 9 reported PLD (see online Appendix 4B).^{218–223,225,228,233} Unpublished^{190,227} and additional data²³⁰ were requested and received for three studies. Two studies could be integrated by reconstructing the published Kaplan-Meier curves.^{232,234} Three studies were excluded because they did not publish survival data,^{224,231} or the proportion of patients in the response categories.⁴¹ Patients reported in the study by Ringdén et al²²⁹ were not included as they had been already included in the data presented by Le Blanc and colleagues.¹⁹⁰ From Lucchini et al,²³³ only four patients with aGvHD stages II-IV were included.

In total, we extracted data from 327 patients from 14 studies to estimate the proportion of individuals in the different health states and the proportion of patients changing between these states (ie, transition probabilities).³¹ Age and sex were only reported for 177 and 152 patients, respectively, which made the originally planned subgroup analysis for age and sex impossible. All patients had aGvHD grades II–IV prior to MSC treatment; for 204 cases, the exact grade was known (18.6% aGvHD II, 45.6% aGvHD III and 35.8% aGvHD IV). Response categories in the underlying studies were defined heterogeneously. Whereas one study did not provide any definition for the response categories employed,³⁷ only complete response (CR =the complete resolution of all aGvHD symptoms) was unanimously defined

in all other studies. Therefore, all response categories other than CR were grouped as “no complete response” (nCR).

Due to the lack of sufficiently detailed observational data, we were forced to use a simplified version of our model simulation. In this version, we could only model the first response to treatment (at day +28) and long-term survival of patients after the first response evaluation to MSCs. The health states sustained response,¹⁹⁰ relapse or persistent aGvHD,¹⁹¹ third-line therapy, chronic GvHD,¹⁹³ relapse or adverse events of haematological disease,¹⁹⁴ and adverse events in general could not be modelled.

Transition probabilities for the first two model cycles

Reported mean and median time of first evaluation was 26.6 and 28 days, respectively (range = 2-58). To integrate all available observations into the model, we assumed that all responses were evaluated within the first 28 days after MSC treatment. Based on this, we calculated a transition matrix showing the probability of response to MSC after day 28 (see Table 1).

Table 1 shows that 43.4% patients with aGvHD II-IV had a CR at first response evaluation whereas 43.7% had nCR, and 12.8% died within the first 28 days.

Table 1 - Transition rates from pre- to post-MSC treatment

		To		
		CR	nCR	Death
From	aGvHD II-IV	43.4%	43.7%	12.8%

Long-term survival estimation

To extrapolate survival estimates beyond study observations, survival data, available for 235 patients (115 CR, 120 nCR), were used. For the excluded cases, the last time of follow-up or time to death was not reported. Patients who died before day 28 were already included in the 28-day transition rates to death. Median survival times were reached at approximately five years (1819 days) for complete responders and at approximately four months (115 days) for nCR.

Kaplan-Meier curves and fitted parametric models for survival are depicted in Figure 2 for both response categories. AIC and BIC values are presented in online Appendix 4C. From a statistical point of view, the fit of the parametric models to the empirical data was similar. Nevertheless, the extrapolation after observation was different. For instance, the extrapolation according to the generalised gamma function predicted that 40% of the CR patients survived more than 25 years after MSC treatment. This was not deemed plausible from a clinical perspective by the experts. Based on clinical expertise, the lognormal distribution would present the best balance between the statistical tests of fit and visual inspection for both CR and nCR.

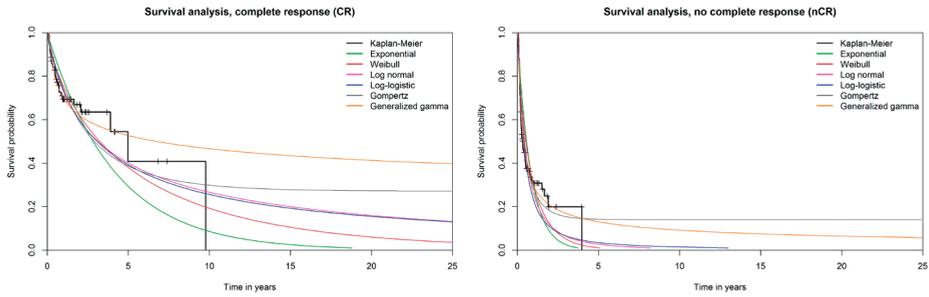


Figure 2 - Empirical Kaplan-Meier curves with parametric model estimations

Results of the model simulation

At the 28-day treatment evaluation, of the 100 simulated cases with aGvHD II-IV, approximately 43 and 44 observations had a CR and nCR, respectively. The median survival time modelled for CR was 3.2 and 0.5 years for nCR. Overall median survival for all patients irrespective of their response category was 9.6 months. Average per-person life-years were

Table 2 - Estimated overall survival probability in per cent

Response category	Years after the first response evaluation							
	1	2	5	10	20	50	80	99
CR	73.1	59.6	40.1	26.7	16.0	6.8	4.1	0
nCR	25.7	11.4	2.6	0.6	0.1	0	0	0
All	43.0	30.9	18.6	11.9	7.0	3.0	1.8	0

Modelling results plotted on empirical Kaplan-Meier (KM) curves

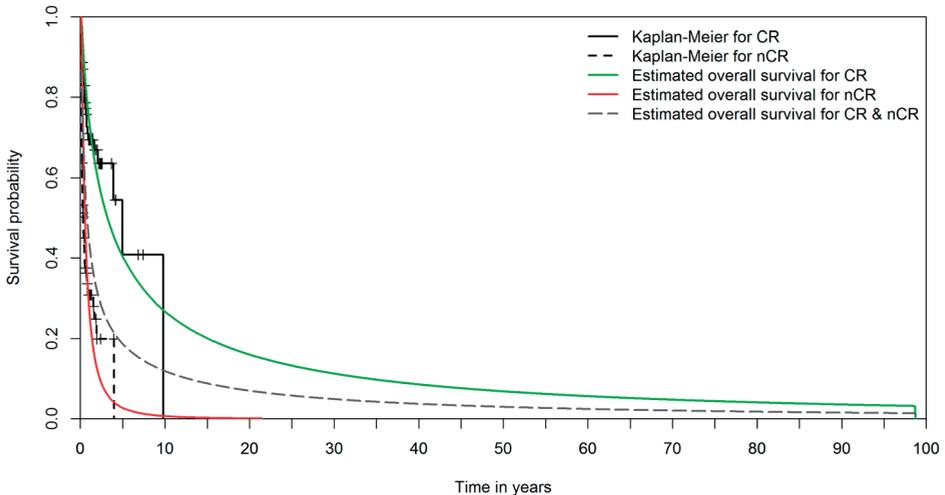


Figure 3 - Modelling results; KM: Kaplan-Meier; Markov trace = simulated, estimated survival of patients over time

estimated at 0.32 years (ie, 3.8 months). In Figure 3, modelling results are plotted on the empirical Kaplan- Meier curves for CR and nCR. Table 2 depicts the estimated overall survival probabilities for different years after the first response evaluation.

DISCUSSION

In this study, we present a DM for the second-line treatment of aGvHD. In line with current recommendations for good modelling practice, we involved an international group of clinical experts to develop this DM and used evidence available from the literature.^{189,191,208,210} Consequently, we ensured that the model sufficiently represents current clinical practice.

The DM can serve manifold purposes. Updated with clinical evidence, it can be used by clinicians and researchers to estimate longterm health outcomes of different treatment alternatives. When costs are added to the clinical evidence, for example, from RETHRIM, economic evaluations can be performed to inform reimbursement decision-makers on the implementation of treatment alternatives.

To run a first model simulation, we searched for available evidence on both costs and clinical evidence on treatment alternatives for aGvHD. We found that MSCs for the treatment of SR-aGvHD are widely studied. Therefore, we were able to integrate more than a decade of empirical data into our DM. Nevertheless, mainly due to the absence of randomised phase III studies, the number of patients included and the restricted follow-up periods, we faced several challenges in integrating the collected information. Consequently, we had made a number of assumptions.

First, MSC products and their administration varied between the studies. With the exception of the study by Fang et al²¹⁸ where MSCs were derived from human adipose tissue, all other studies used bone marrow-derived products. In addition, the number of MSC infusions (between 1 and 21 infusions) as well as the dosage of infused MSCs (between 0.6 and 20 x10⁶ cells per kg body weight) varied across the studies. In this regard, we assumed that type and administration of MSC products had no effect on transition probabilities or mortality rates. Whereas this made the integration of the study results possible, the data did not allow for further stratification to test potential MSC derivation-related or dose-related effects on the response rates.

Second, there were not enough data available to estimate transitions between response categories after a first response evaluation. We had assumed survival can be predicted based on the initial response category at 28 days post-MSc transfusion. However, in clinical practice response categories may change in any direction after the first evaluation. Of the included studies, only Prasad et al³⁶ assessed response to MSCs in paediatric patients more than once. In this study, five of twelve patients further improved after day 32 to a complete remission. Future studies measuring response on several time points after MSC treatment

could inform our model on subsequent changes in response categories. Whereas this enables a better estimate for subgroups, the effect on the average survival of the entire population is most likely negligible.

Third, it needs to be noted that the simulation did not consider the underlying haematological disease, nor the patients' age or sex. This choice was made as not all studies did report on these variables and any further stratification would have resulted in a reduction in the population on which the different estimates are based. However, we acknowledge that the underlying haematological disease and age and sex can be important determinants for long-term survival. Detailed reporting on patient characteristics and their diagnosis may help to enable further analyses for these subgroups.

Our modelling results, however, did show the expected longer survival after MSC transfusion for patients that achieved CR at first response evaluation, when compared to patients with nCR. These estimates are in line with previous findings highlighting the importance of complete response for long-term survival.^{235–240}

To our knowledge, there are no long-term survival results published for SR-aGvHD patients treated with MSCs other than the two reports^{241,242} that are based on studies^{190,229} included in our study. Therefore, we attempted to compare our results to survival estimates of studies that tested other second-line treatment options for aGvHD. To find suitable studies, we consulted the most recent NHS England clinical commissioning policy on the treatments for GvHD following HSCT.¹⁹⁵ This guideline is based on an extensive and updated review of the literature and concludes that there is sufficient evidence only for extracorporeal photopheresis (ECP) to be routinely commissioned for the treatment of aGvHD. Therefore, we focussed on a comparison with ECP. For other treatment options such as infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or MSCs, the reviewers found that there was no sufficient evidence available to propose the routine commissioning for aGvHD.

Regarding survival of aGvHD patients treated with ECP, the largest series was published by Greinix et al.²³⁸ in a phase II prospective study.¹⁹⁵ Every week, 59 patients with steroid-refractory or steroid-dependent GvHD received two consecutive ECP treatments. CR and nCR was defined as in our study. The reported median survival was below 6 months after HSCT for patients with nCR, confirming our median survival estimations for nCR to MSC of approximately 6 months.²³⁸ In the study of Greinix et al,²³⁸ median survival for complete responders was never reached during the reported follow-up period of 9 years after HSCT. For this study, this implies that the probability of surviving nine years after HSCT would be approximately 59% for patients with a CR. With an estimate of approximately 27% at ten years post-MSCs, our estimates for patients with a CR are significantly lower. This may be explained by differences in patient population before treatment (ie, Greinix et al.²³⁸ included a higher number of patients with aGvHD grade II (61%)). In addition, the study by Greinix and colleagues was based on a limited amount of complete responders (n = 41).

Although we were able to demonstrate longer survival for patients with CR when compared to nCR, the relatively high mortality rate of SR-aGvHD, even with MSCs, can still be regarded as unacceptably high. And although there were numerous studies reporting on MSCs as a treatment alternative for SR-aGvHD, none of them included patient-reported outcomes (PROs) such as HRQoL. Updating our results with HOVON113 findings, including HRQoL measures, might improve the current survival estimates and show favourable treatment outcomes in terms of quality of life for MSCs when compared to placebo. However, until these study results are presented, this remains subject to speculation and the search for alternative (pre)treatments helping patients to achieve a complete response will have to continue.

CONCLUSION

The designed DM provides a comprehensive overview on the second-line treatment pathways for aGvHD in general. The model simulation with data from previously published studies on MSCs as a second-line treatment option for aGvHD presented outcomes matching the literature as well as clinical expectations. This demonstrates the practicability and usefulness of the model. However, to date, only insufficiently detailed data are available to fully model all health states and to perform a cost-effectiveness analysis. The yet restricted model simulation would therefore benefit from additional data, preferably from a phase III RCT. The integration of effectiveness results together with health-related quality of life measures (e.g., from the EQ-5D questionnaires) and different cost components derived from the RETHRIM trial could overcome this limitation and enable a full cost-utility analysis.

PART II

**Cost-utility of novel treatments in
haemato-oncology**

Chapter 5

Cost-Effectiveness of Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-cell acute Lymphoblastic Leukemia. A societal view

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ABSTRACT

Introduction: In several studies, tisagenlecleucel demonstrated encouraging rates of remission and lasting survival benefits in paediatric patients with relapsed/refractory acute lymphoblastic leukemia ALL. We assessed its cost-effectiveness (list price: 320,000 EUR) when compared to clofarabine monotherapy (Clo-M), clofarabine combination therapy (Clo-C), and blinatumomab (Blin) from both a healthcare and a societal perspective and considered future medical and non-medical consumption costs.

Methods: With a three-state partitioned survival model we simulated a cohort of paediatric patients (age: 12 years) through different disease states until death. Relevant outcomes were life years, quality-adjusted life years (QALYs), healthcare costs, societal costs and the incremental cost-effectiveness ratio (ICER). Uncertainty was explored through deterministic and probabilistic sensitivity analyzes and several scenarios.

Results: Total discounted costs for tisagenlecleucel were 552,679 EUR from a societal, and 409,563 EUR from a healthcare perspective. Total discounted societal costs for the comparator regimens ranged between 160,803 EUR for Clo-M and 267,259 EUR for Blina. Highest QALYs were estimated for tisagenlecleucel (11.26), followed by Blina (2.25), Clo-C (1.70) and Clo-M (0.74). Discounted societal ICERs of tisagenlecleucel ranged between 31,682 EUR/QALY (Blina) and 37,531 EUR/QALY (Clo-C) and were considered cost-effective with a willingness-to-pay (WTP) threshold of 80,000 EUR/QALY. None of the scenarios exceeded this threshold and more than 98% of the iterations in the probabilistic sensitivity analysis were cost-effective.

Discussion: At the current price tisagenlecleucel is cost-effective from both a healthcare and a societal perspective. Nevertheless, long-term effectiveness data is needed to validate the necessary assumptions.

INTRODUCTION

With current first-line treatment protocols, survival in pediatric B-cell acute lymphoblastic leukemia (pALL) increased to 85-90% over the past years. Also in relapsed pALL, 40-60% of children can be cured with intensive chemotherapy regimens, often including allogeneic stem cell transplantation (alloSCT).²⁴³ The prognosis for patients with a second relapse, with a relapse after alloSCT or with refractory pALL remains however poor, ranging from 10-30% two-year overall survival (OS).^{244,245} In this article, these patients are referred to as r/r pALL patients. Current regimens for r/r pALL include clofarabine monotherapy (Clo-M), clofarabine combination therapy (Clo-C), and blinatumomab (Blina), although no clearly defined standard of care yet exists. In countries such as the US and the UK, salvage chemotherapy is also commonly used.

In several clinical trials, the chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel showed high rates of remission²⁴⁶⁻²⁵⁰ and lasting survival benefits with 12-month event-free survival (EFS) rates between 45% to 51%.^{246,247,249} These promising results come at a high costs however. In the US tisagenlecleucel was made available at 475,000 USD (approx. 414,000 EUR) which included an outcome-based commercial model.²⁵¹ The stated list price in the UK is 282,000 GBP (314,000 EUR; 360,000 USD) and after a confidential discount it is currently available via the Cancer Drug Fund.²⁵² In the Netherlands, the list price is 320,000 EUR. Whether tisagenlecleucel is a cost-effective alternative to existing treatments is a pressing question for policymakers, payers, clinicians as well as patients, and can be explored by cost-effectiveness modelling approaches.²⁵³ Ideally, such a cost-effectiveness analysis is not limited to a healthcare (or payer) perspective, including only direct healthcare costs. This is because treatment for r/r pALL also affects both personal and professional lives of the patients and their caretakers. When other aspects such as travel costs, informal care costs and productivity losses or gains are incorporated, a cost-effectiveness study is referred to as being conducted from a so-called “societal perspective”. The Dutch EE guideline recommends such a perspective for all cost-effectiveness analyses in the Netherlands.⁴²

To date, some economic evaluation studies have been performed estimating the cost-effectiveness of tisagenlecleucel compared to Clo-M, Clo-C or Blin over a lifetime horizon (i.e. until all simulated patients died).²⁵⁴⁻²⁵⁸ All of them found tisagenlecleucel cost-effective in at least one scenario from a payer perspective^{255,257,258} and a societal perspective.^{254,256} To employ a societal perspective, Sarkar et al.²⁵⁴ included cost of caregivers, patient time, transportation and parking, as well as meals. However, it remains unclear what specific cost items were considered with regard to caregivers and patient time. The initial manufacturer submission to the Canadian Agency for Drugs and Technologies in Health (CADTH) did not seem to include a societal perspective. Therefore, the CADTH considered travel and accommodation time for patients and caregivers, medical coinsurance amounts, copayment, and deductibles over a period of only three years for a scenario analysis from a societal

perspective.²⁵⁶ Assuming a lifetime horizon for the economic model, the considered total societal costs for tisagenlecleucel of approximately 16,500 CAD seem to be a drastic underestimation of the true societal costs that can be attributed to tisagenlecleucel in the lifetime of paediatric patients.

Our aim was to add to the existing evidence for tisagenlecleucel in *r/r* pALL patients by estimating the cost-effectiveness of tisagenlecleucel for paediatric patients with *r/r* pALL from a broad societal perspective when compared to Clo-C, Clo-M, and Blina, respectively. We are the first study to consider both medical and non-medical consumption costs in life years gained (i.e. future medical costs). Furthermore, we considered productivity losses for patients' caretakers rather than for the paediatric patients and explored the inclusion of potential productivity gains for children with long-term EFS.

METHODS

The primary outcome of this analysis was the incremental cost-effectiveness ratio (ICER) of tisagenlecleucel for each comparator from two perspectives over a lifetime horizon.⁴² A healthcare perspective included costs and effects of pre-treatment, treatment, adverse events, follow-up period, subsequent HSCT and future medical costs. A societal perspective included all costs and effects of the healthcare perspective in addition to costs for travel, the stay of caregivers at a charity hotel during treatment, productivity losses of patients' caregivers, and informal care. Lastly, we also considered non-medical consumption costs.^{259,260} Results of all perspectives are reported separately. The base-case is defined from a societal perspective, including future non-medical consumption costs as this represents the most conservative estimates.

To estimate the clinical effectiveness outcomes such as life years (LYs) and quality-adjusted life-years (QALYs) of each treatment, we modelled a fictive cohort of paediatric patients (12 years of age) that receive tisagenlecleucel or either comparator treatment (i.e. Clo-M, Clo-C, or Blina). At any time, the modelled patients could be in one of the three health states: (i) EFS, (ii) progressive disease (PD) or (iii) death (see Figure 1). The proportion of patients per health state was estimated from standard parametric survival functions (i.e. exponential, Weibull, log-logistic, log-normal, Gompertz and generalised Gamma) with the best statistical and clinical fit to the observed OS and EFS.²¹¹ In addition, a set of flexible cubic spline models was considered to capture the potential curative nature of tisagenlecleucel.²⁶¹ Statistical fit was assessed with Akaike information criterion (AIC) and the Bayesian information criteria (BIC), while clinical plausibility was validated by a clinical expert (PMH). For tisagenlecleucel, survival (EFS and OS) was based on pooled data (N=193) from the ELIANA (NCT02435849), ENSIGN (NCT02228096), and B2101J (NCT01626495) trials.²⁶²⁻²⁶⁴ Overall survival for Clo-M,²⁶⁵ Clo-C,²⁶⁶ and Blina²⁴⁵ was based on the literature.

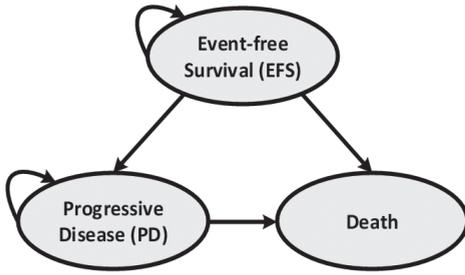


Figure 1 – De novo model

Since EFS data were not available for the comparator arms, EFS was considered proportional to OS, using a validated ratio from the literature.²⁶⁷

Patients who remained in the EFS state after five years were assumed to be long-term survivors of ALL (i.e. considered cured). This assumption was based on the observed plateau phase and validated by expert opinion. OS of these patients was modelled by applying the standard mortality rate (SMR) of 15.2 for 5-year ALL survivors.²⁶⁸ The initial proportional relationship of EFS to OS was assumed for the first five years of the model. After the fifth year, the cumulative survival probabilities of EFS were assumed to flatten up until they reached OS. In the model, EFS could not exceed OS at any time point. Furthermore, we assumed that relapses and leukaemia-specific deaths only occurred within the first 5 years for all comparators.

The model cycle length was set to one month. To adhere to the Dutch guideline for economic evaluation research (Dutch EE guideline), costs and effects were discounted at a 4% and 1.5% rate, respectively.^{42,269}

Tisagenlecleucel was included as a one-time infusion costing 320,000 EUR and its dosing schedule was according to the ELIANA trial.²⁶² For the comparator treatments, dosing schedules were taken from the literature.^{245,266,270} Adverse treatment events (AEs) were considered for all treatments and included cytokine release syndrome and B-cell aplasia. After initial therapy, we assumed that a proportion of patients would receive HSCT (17%, 16%, 40%, and 34% for tisagenlecleucel, Clo-M, Clo-C, Blina, respectively). For patients staying alive (i.e. in EFS or PD) we assumed follow-up costs for outpatients visits and laboratory test and procedures with different resource use frequencies per model health state (see online Appendix 5H).

To calculate QALYs, health-state utilities for EFS and PD were derived from the EQ-5D-3L data collected in the ELIANA trial and estimated with the Dutch tariff.^{262,271} Additional disutilities (i.e. for treatment and adverse events) and age-related utility decrements were based on the literature.^{272–274}

Prices and costs for the societal perspective were based on the Dutch EE guideline and the literature (see Table 1 and online Appendix 5B).^{42,275} Future costs (medical and non-medical consumption) were based on the PAID tool (version 3.0).²⁷⁶ Furthermore, we explored

potential productivity gains due to the improved survival by assuming that 53% of the long-term survivors aged 18 years or older would be employed.²⁷⁷ These cost savings were explored in a scenario analysis to account for potential future productivity gains.

Lastly, we conducted deterministic sensitivity analyses (DSA), probabilistic sensitivity analysis (PSA) to address uncertainty of the model input parameters and estimates (see online Appendix 5A). Several scenario analyses were performed to explore the influence of different assumptions on the ICER.

A list of key input parameters to the model including their source is presented in Table 1 and a more detailed description of the employed methodology can be found in the online Appendix.

Table 1 - Model input parameters and values

Variable	Value	Measurement of uncertainty in DSA and PSA	Distribution used in PSA	Source	
Model settings	Discount rate (costs)	NA	NA	Dutch EE guideline ^{e2}	
	Discount rate (benefits)	4.00%	NA		
	Time horizon	1.5%	NA	NA	
Patient characteristics	Starting age (years)	88 years	NA	NA	
	Percent female	12	95% CI: 1; 25	Normal	
	Mean body surface area (BSA)	46.63%	SE: 0.04	Beta	
	Mean weight (kg)	1.3	SE: 0.03	Normal	
	OS distribution	41.7	SE: 1.52	Normal	
Efficacy	OS distribution	Log normal	Different distributions selected in DSA	Assumption validated by clinical expert	
	EFS distribution	Gompertz	Bootstrapped		
	Duration of benefit in months	60	NA		NA
	EFS vs OS ratio for all comparators	0.69	SE: 25% of mean		Beta
Drug and procedure acquisition cost	Pre-treatment cost for lymphodepleting regimen	521 EUR		Van den Berg et al., 2011	
	Tisagenlecleucel	320,000 EUR		ELIANA trial (resource use); Dutch Z-index (unit cost)	
	Clofarabine monotherapy	71,020 EUR	SE: 25% of mean	Gamma	
	Clofarabine combination therapy	35,453 EUR		Dutch Z-index public list price	
Blinatumomab		117,934 EUR		Jeha et al. 2006 (dosing schedule); Dutch Z-index (unit cost)	
				Hijjya et al. 2011 (dosing schedule); Dutch Z-index (unit cost)	
				von Stackelberg 2016 (dosing schedule); Dutch Z-index (unit cost)	

Table 1 - Model input parameters and values (*continued*)

Variable	Value	Measurement of uncertainty in DSA and PSA	Distribution used in PSA	Source
Pre-treatment cost for lymphodepleting regimen	6,301 EUR			ELANA (resource use); Dutch EE guideline and Franken et al., (unit cost inpatient and daycare respectively)
Tisagenlecleucel	15,932 EUR			
Inpatient and outpatient administration cost	Clofarabine monotherapy	2,437 EUR	SE: 25% of mean	Clinical expert opinion (resource use); Franken et al., 2018 (unit cost)
	Clofarabine combination therapy	4,292 EUR	Gamma	
Blinatumomab	1,997 EUR			Clinical expert opinion (resource use); Dutch EE guideline (unit cost)
Rates for tisagenlecleucel	16.58%	SE: 25% of mean		Clinical expert opinion (resource use); Franken et al., 2018 (unit cost); von Stackelberg et al. 2016 (distribution of patients over treatment cycles)
Rate for clofarabine monotherapy	16.39%	SE: 0.07		pooled data, (duration and percentage)
Rate for clofarabine combination therapy	40.00%	SE: 0.05	Beta	Evoltra product label (duration and percentage) Hijjya et al. 2011 (duration and percentage)
Subsequent HSCT	Rate for blinatumomab	34.29%	SE: 0.10	von Stackelberg et al. 2016 (duration and percentage)
Disutility (treatment)	-0.21			Forsythe et al., 2018
Disutility (6-12 months after treatment)	-0.02	SE: 25% of mean	Beta	
Costs: stem cell harvesting ^a	66,581 EUR			Blommestein et al., 2012
Costs: initial HSCT procedure ^a	44,391 EUR	SE: 25% of mean	Gamma	
Follow-up costs after HSCT (up to one year) ^a	106,618 EUR			

Table 1 - Model input parameters and values (continued)

Variable	Value	Measurement of uncertainty in DSA and PSA	Distribution used in PSA	Source
Utility for EFS	0.83	SE: 0.03		ELIANA trial
Utility for PD	0.68	SE 0.05		
Disutility for tisagenlecleucel (duration in days)	-0.20 (26)			
Disutility for Clo-M (duration in days)	-0.20 (66)			Kwon et al. 2018 (utility value); ²⁷³
Disutility for Clo-C therapy (duration in days)	-0.20 (47)	SE: 25% of mean	Beta	Gaynon et al. 2006 (duration Clo-M); ²⁷⁸ Hijiya et al. 2011 (duration (Clo-C)); ³⁶⁶ von Stackelberg et al. 2016 (duration Blina) ²⁴⁵
Disutility for Blina (duration in days)	-0.20 (61)			Janssen et al. 2014 ²⁷⁴
Age-related utilities	Age < 25: 0.95 Age 25-74: 0.93 - 0.89 Age 75+: 0.83		NA	
Future medical costs	Various costs per treatment and age group		NA	Van Baal et al., 2011 ²⁶⁰
Future non-medical (consumption) costs	Various costs per treatment and age group		NA	

Table 1 - Model input parameters and values (*continued*)

Variable	Value	Measurement of uncertainty in DSA and PSA	Distribution used in PSA	Source
Patient and family costs	Distance to hospital	79 kilometers	NA	Own calculation
	Travel costs ^b	3.09 EUR parking costs per visit, 0.19 EUR per kilometer for travelling by car	NA	Dutch EE guideline ⁴²
	Average number of caregivers / parents accompanying patient	1.5	NA	Expert opinion
	Parents stay at a charity hotel during treatment	60 EUR	NA	Charity hotel website (Ronald McDonald)
Productivity losses	Informal care ^c	14.52 EUR per hour, 8 hours per outpatient visit, daycare treatment, or inpatient hospital day	NA	Dutch EE guideline ⁴²
	Total productivity losses females	12,499 EUR		Dutch EE guideline ⁴² (wage per hour)
	Total productivity losses males	8,993 EUR		
Productivity losses	Rate of females with productivity losses	60%	SE; 25% of mean ^b	Hovén et al., 2013 ²⁷⁵ (proportion of parents going back to work) Statistics Netherlands (proportion of parents contributing to the laborforce)
	Rate of males with productivity losses	85%		

Allo-SCT, allogeneic stem cell transplantation; CI, confidence interval; MUD, matched unrelated donor; NA, not applicable; SE, standard error; sib, sibling donor; UCB, umbilical cord blood

a. Based on proportions for different HSCT type (see online Appendix)

b. The amount of travel trips is dependent on the assumed treatment regimen and respective number of visits during treatment and follow-up visits (see online Appendix for treatment schedules and follow-up visit frequencies)

c. Informal care was assumed for patients aged < 18 years

d. Only total costs of the productivity losses were varied in both DSA and PSA (i.e. a combination of the rate and the costs)

RESULTS

In the model base case, tisagenlecleucel yielded 14.01 discounted LYs and 11.26 discounted QALYs, which was much higher than any of the comparators. Undiscounted LYs and QALYs were 18.98 and 15.21, respectively. Figure 2 shows the observed EFS from the pooled data as well as the modelled EFS of all treatments. Figure 3 shows both observed and modelled OS of all treatments.

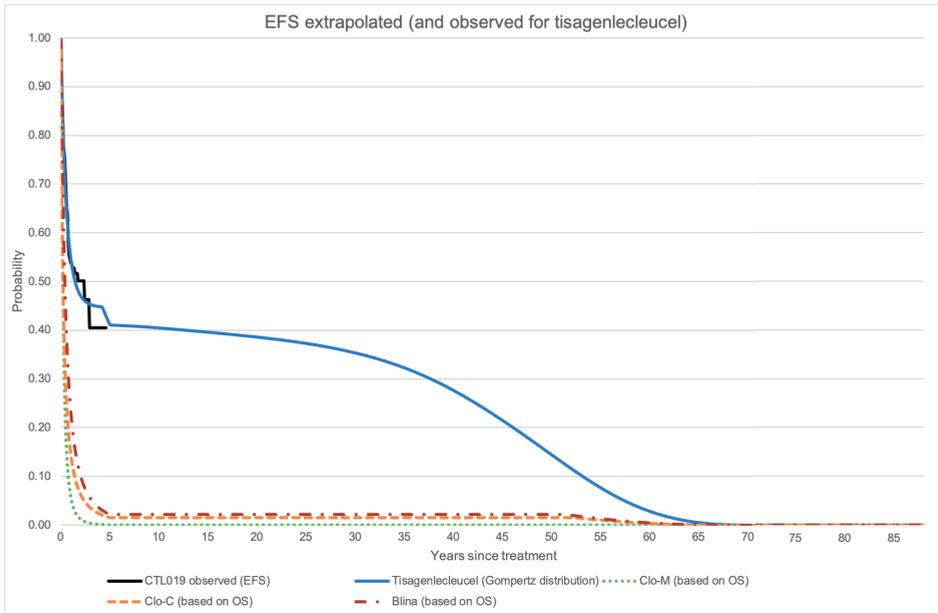


Figure 2 – EFS extrapolated (and observed for tisagenlecleucel)

The total discounted treatment costs for tisagenlecleucel were 338,122 EUR and included costs for drug acquisition and administration as well as outpatient and inpatient days. These costs were the highest when compared to any comparator regimen (Clo-M: 73,457 EUR, Clo-C: 39,745 EUR, Blina: 119,931 EUR). The main cost driver were the much higher drug acquisition costs for tisagenlecleucel (320,000 EUR), when compared to all other drugs (See table 1). Only for tisagenlecleucel was a pre-treatment regimen (i.e. lymphodepleting regimen) necessary. Total discounted costs for this pre-treatment were 6,821 EUR, with drug acquisition costs (i.e. for fludarabine, cyclophosphamide, cytarabine, or etoposide) being the main cost driver. Considering both pre-treatment and treatment costs of tisagenlecleucel together, the total treatment costs amounted to 344,943 EUR (discounted). Discounted costs for adverse events were highest for tisagenlecleucel (24,731 EUR), when compared to

Clo-M (4,269 EUR), Clo-C (8,085 EUR), and Blina (4,210 EUR). This was mainly due to the relatively high prevalence of B-cell aplasia and the associated high costs of IVIG.

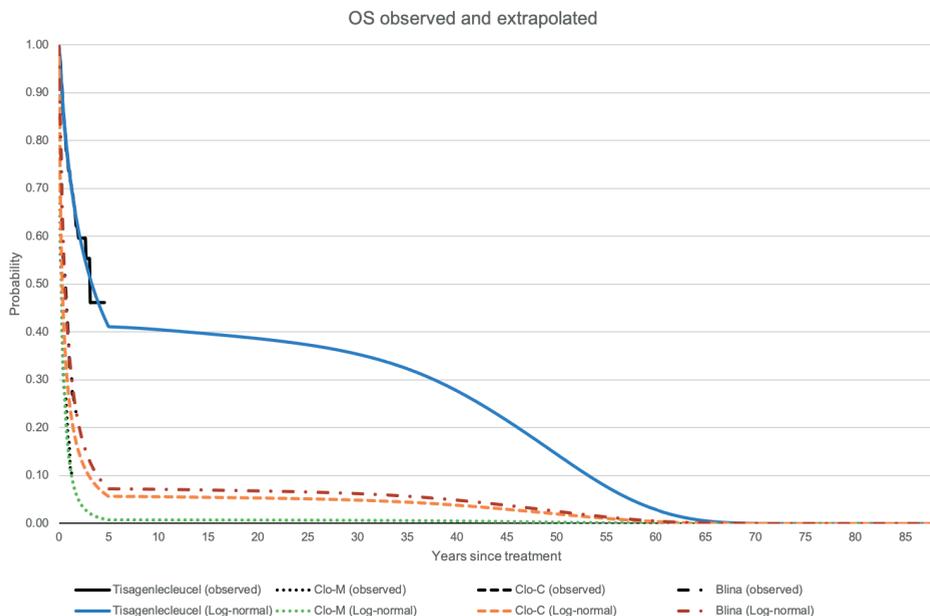


Figure 3 - OS observed and extrapolated

From a healthcare perspective, considering all discounted cost for treatment (including pre-treatment for tisagenlecleucel), adverse events, follow-up period, subsequent HSCT and future medical costs of unrelated diseases, the total healthcare costs for tisagenlecleucel was 409,563 EUR. This was nearly four times as much when compared to Clo-M (113,937 UER) or Clo-C (136,069 EUR) and more than double the total healthcare costs of Blina (200,293 EUR).

For a societal perspective, we added costs of caretakers' productivity losses, travel costs (for both caretakers and patients), informal care for patient below the age of 18 years, and caretakers' stay at a charity hospital during the treatment period to the healthcare perspective. The total discounted costs from this perspective were 488,340 EUR for tisagenleucel, and 156,909 EUR, 182,496 EUR and 253,024 EUR for Clo-M, Clo-C, and Blina, respectively. Major cost drivers in all perspectives were the total costs of treatment for tisagenlecleucel, Clo-M, and Blina. Only for Clo-C, subsequent HSCT was more expensive than the treatment costs. When non-medical consumption costs were added to the societal perspective, total costs increased for all treatment options. Total discounted costs for tisagenlecleucel,

Clo-M, Clo-C, and Blina were 552,679 EUR, 160,803 EUR, 193,920 EUR, and 267,259 EUR, respectively.

When comparing total discounted costs of the healthcare perspective to the societal perspective, costs increased most for tisagenlecleucel (78,777 EUR), followed by Blina (42,972 EUR), Clo-C (46,427 EUR), and Clo-M (52,731 EUR). Considering future non-medical consumption as part of the societal perspective, the additional costs when compared to the healthcare perspective were 143,116 EUR, 66,966 EUR, 57,851 EUR, and 46,866 EUR for tisagenlecleucel, Clo-M, Clo-C, and blina, respectively.

The discounted ICERs per QALY gained, comparing tisagenlecleucel to Clo-M, Clo-C, and Blina from a healthcare perspective were 27,443 EUR, 28,611 EUR, and 23,229 EUR, respectively. When taking a societal perspective, the ICERs increased to 30,767 EUR/QALY, 31,996 EUR/QALY, and 26,120 EUR/QALY comparing tisagenlecleucel to Clo-M, Clo-C, and Blina, respectively. When future non-medical consumption costs were added, ICERs of tisagenlecleucel compared to Clo-M, Clo-C, and Blina were 36,378 EUR/QALY, 37,531 EUR/QALY, and 31,682 EUR/QALY. Assuming a WTP-threshold of 80,000 EUR/QALY gained, it can thus be concluded that tisagenlecleucel is a cost-effective treatment when compared to any comparator examined in this study.

The estimation of potential lifetime productivity gains could be 202,563 EUR, 482 EUR, 8,884 EUR, and 12,658 EUR per patient for tisagenlecleucel, Clo-M, Clo-C, and Blina. However, it needs to be noted that these estimates are subject to substantial uncertainty as explained in the discussion and are therefore not considered for any presented ICER.

All deterministic results of the cost-effectiveness analysis are presented in Table 2.

Table 2 - Deterministic results of the model base case

Item	Treatment			
	Tisagenlecleucel	Clofarabine monotherapy	Clofarabine combination therapy	Blinatumomab
Costs in EUR				
Pre-treatment	6,821	-	-	-
Treatment ^a	338,122	73,457	39,745	119,931
Adverse events	24,731	4,269	8,085	4,210
Follow-up	3,811	540	1,204	1,549
Subsequent HSCT	36,077	35,670	87,036	74,602
Patient and family	14,277	2,627	2,733	3,319
Productivity losses	28,301	25,868	26,857	30,696
Future medical costs (unrelated disease and consumption)	100,538	18,371	28,262	32,952
Total costs	552,679	160,803	193,920	267,259
Effects				
Life years	14.01	0.74	2.46	3.17
Quality-adjusted life years	11.26	0.49	1.70	2.25
Increments (<i>tisagenlecleucel versus each comparator</i>)				
Costs in EUR	-	391,876	358,759	285,420
Life years	-	13.27	11.55	10.84
Quality adjusted life years	-	10.77	9.56	9.01
ICERs				
Costs (in EUR) per life years gained	-	29,535	31,052	26,334
Costs (in EUR) per quality-adjusted life year gained	-	36,378	37,531	31,682

^aThe treatment costs entail drug/procedure costs, and costs for the inpatient and outpatient visits

Deterministic sensitivity analyses demonstrated that the variation of the starting age of the simulated cohort was the most influential factor for the ICER in all three comparators. Figure 4 depicts the top 10 DSA results of ICERs per QALY for each comparator treatment in so-called Tornado diagrams. Although the change in some parameters affected the ICER quite heavily, none of the calculation exceeded an ICER of 45,000 EUR per QALY gained. The impact of choosing different parametric survival models for OS and EFS and the impact of choosing different time horizons were tested in scenario analyses. Depending on the chosen parametric survival function for EFS, different proportions of cured patients were estimated. In this case, we refer to cured patients as those who stay in EFS five years after treatment until the end of life. The proportion of cured patients five years post-treatment varied between 8% (exponential distribution for EFS) and 40% (log-normal distribution). Choosing either parametric survival function (both for OS or EFS) did not cause the ICER to exceed the WTP threshold of 80,000 EUR per QALY gained.

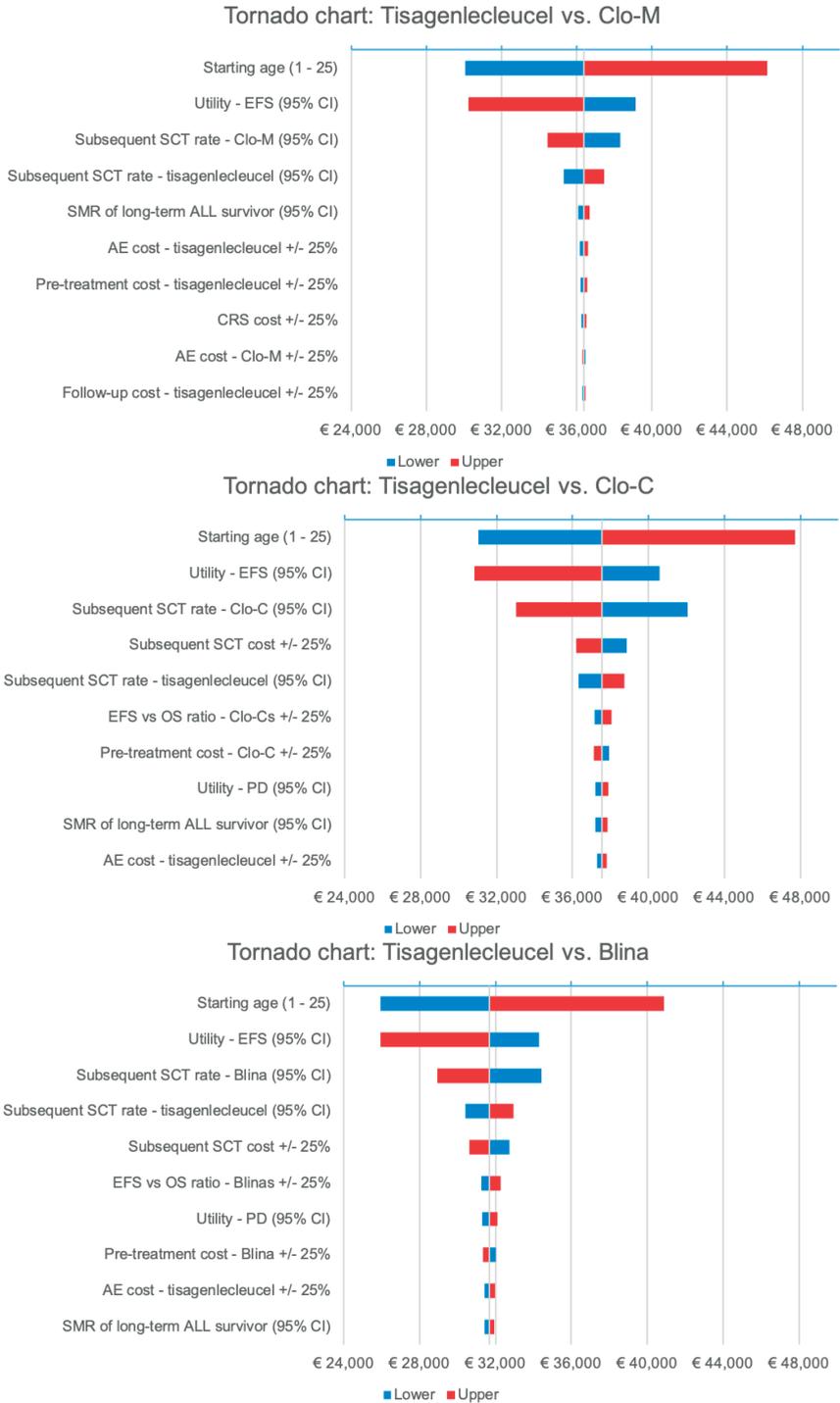


Figure 4

Results of the 5,000 PSA iterations (societal perspective, including future non-medical consumption) are depicted in the cost-effectiveness (CE) plane in Figure 5. The average ICERs per QALY gained were in line with the deterministic results with 38,129 EUR, 42,289 EUR, and 34,564 EUR when compared to Clo-M, Clo-C, and Blina, respectively. At a WTP-threshold of 80,000 EUR, the probability of all simulations being cost-effective for Clo-M, Clo-C, and Blina was 100%, 98%, and 100%, respectively.

Of the conducted scenario analyses, assuming a time horizon of twenty years had the highest impact on the ICER. In this scenario, the ICERs per QALY gained increased to 60,859 EUR, 63,341 EUR, and 53,698 EUR for Clo-M, Clo-C, and Blina, respectively. This implies that tisagenlecleucel is less cost-effective with a shorter time horizon.

Assuming a plateau phase in EFS after three years (instead of five years) decreased the ICER per QALY gained to 31,798 EUR, 33,641 EUR, and 29,219 EUR for Clo-M, Clo-C, and Blina, respectively. This suggests that the sooner patients can be considered cured with tisagenlecleucel, the more cost-effective the treatment is.

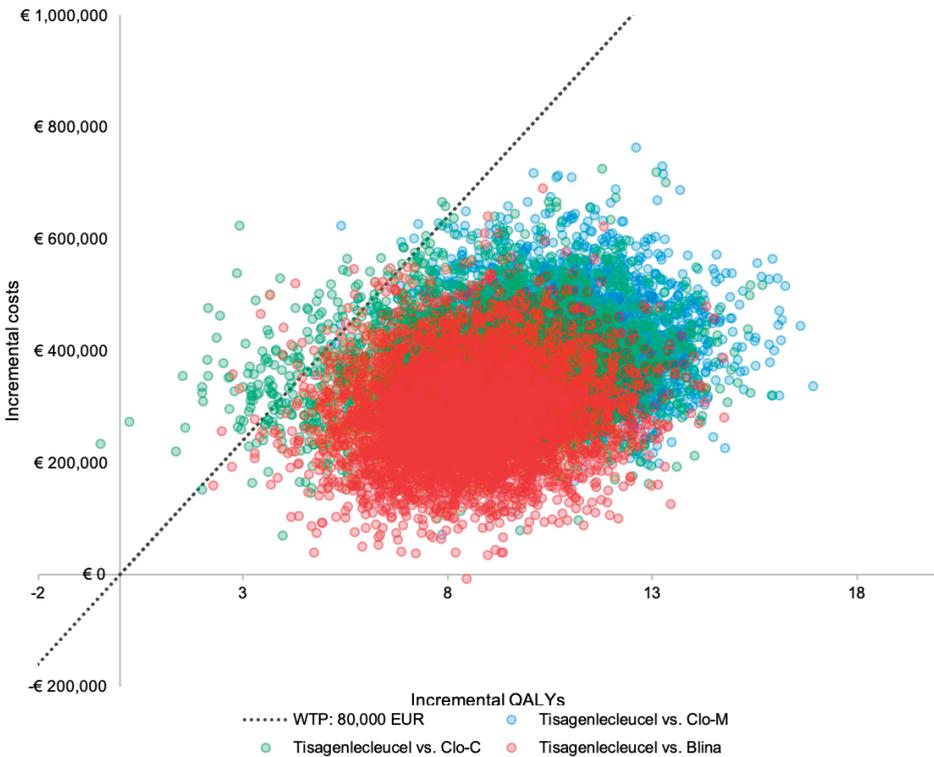


Figure 5

Our analyses also show that the prevalence of B-cell aplasia substantially adds to the costs of the tisagenlecleucel treatment, mainly through the length of IVIG usage. Based on the literature, we assumed an average duration of B-cell aplasia of 11.4 months. Testing this assumption in a scenario analysis and considering IVIG cost for the entire duration of EFS among those without subsequent HSCT, increased the ICER to 49,969 EUR/QALY, 52,847 EUR/QALY, and 47,932 EUR/QALY gained for Clo-M, Clo-C, and Blina, respectively. Hence, a longer treatment duration with IVIG negatively affected the ICER.

DISCUSSION

Our results showed that assessing the cost-effectiveness of tisagenlecleucel from a societal perspective as opposed to a healthcare perspective, increased all estimated total costs and ICERs. This was due to the relative higher increase in total costs for tisagenlecleucel when compared to Clo-M, Clo-C, or Blina. Nevertheless, we demonstrate that tisagenlecleucel is also cost-effective for pediatric patients with relapsed/refractory B-cell acute lymphoblastic leukemia from a societal perspective. Although all efficacy input parameters for the model stem from international clinical studies, background mortality and HRQoL data as well as all costs were analysed from a Dutch perspective. Transferability to an international setting needs therefore to be considered with caution.

Nevertheless, considering all assumptions made, our model results can be regarded as robust: all explored scenarios rendered tisagenlecleucel cost-effective with a WTP-threshold of 80,000 EUR per QALY gained. In addition, all 5,000 iterations of the PSA yielded a probability for tisagenlecleucel being cost-effective of more than 98%. The deterministic sensitivity analysis showed that the cohort starting age, together with the utility values for EFS and the assumed subsequent HSCT rates for the comparator treatment had the highest impact on the results. However, when any of these parameters were altered (i.e. increased or decreased in their estimated value), none of them had the potential to bring the ICER above 48,000 EUR/QALY gained. Lastly, the conducted scenario analyses demonstrate an increase in the ICER with decreasing time horizons (i.e. follow-up time) and a considerable impact of the IVIG assumption (i.e. how long IVIG is given) on the ICER.

The favourable results for tisagenlecleucel in our analysis can mainly be explained by the extensive survival gains when compared to other treatment options. With a total of 14.01 life years (discounted), tisagenlecleucel performed significantly better than any of the comparators. Since to date no randomized clinical trials for tisagenlecleucel in r/r ALL patients exist, the modelled effectiveness was based on single-arm studies. Furthermore, no information about EFS was available in the publications of the comparative treatments. Based on a high correlation between EFS and OS,²⁸⁰ we assumed that the missing EFS

data could be estimated based on the available OS data. This may have influenced the EFS estimates of the comparative treatments.

According to the currently available evidence, tisagenlecleucel is a potential curative treatment thereby preventing young patients from premature death. Consequently, substantial life years and QALYs can be gained from a lifetime perspective. However, it needs to be noted that the long-term effects of tisagenlecleucel are not yet captured by any study, registry or clinical trial, because none of those have life-time follow-up data. We assumed no specific late side effects after tisagenlecleucel and regarded patients to be cured after five years. In our model, patients that remain in EFS for five years after treatment are considered being cured. This assumption helped to reduce some of the long-term uncertainties arising from long-term survival extrapolation data beyond the observed trial data. The five-year cut-off was validated by clinical experts and our approach was similar to the one used for the National Institute for Health and Care Excellence (NICE) mock technology appraisal for chimeric antigen receptor T-cell (CAR-T) therapy as a treatment for r/r B-cell pALL.³⁸ However, the exact time at which patients in long-term EFS may be considered cured is uncertain. In a scenario analysis we explored the impact of assuming three instead of five years as a cut-off. Consequently, all ICERs decreased (ICER Clo-M: 29,628 EUR/QALY, ICER Clo-C: 31,459 EUR/QALY, ICER Blina: 27,110 EUR/QALY gained), meaning that the sooner patients can be considered cured, the more cost-effective tisagenlecleucel is. Irrespective of the time point at which patient may be considered cured, it is uncertain what fraction of patients can be considered disease free at that time. Up until the five years after treatment, the EFS in the model was based on parametric survival functions. Each of these functions estimated different probabilities for EFS five years after treatment start. These estimates ranged between 8% and 40% for EFS, but none of these scenarios exceeded an ICER of 45,000 EUR per QALY gained. Nonetheless, empirical long-term follow-up data are vital to reduce uncertainty in effectiveness outcomes. Data from patient registries such as the EBMT (European Society for Blood and Marrow Transplantation) registry may play a vital role in collecting the necessary information.

The estimated favourable survival outcomes (both in EFS and OS) indicate significant benefits for both patients and society. These can best be captured by extending the healthcare perspective to a societal perspective. Assuming a societal perspective made it possible to capture costs from a broad economic angle, including the impact of the treatment on patients and their families. To include these additional cost components, health economic researchers can choose from an abundance of validated methodological approaches in the literature or health economic guidelines. However, most of the available approaches only focus on adult patient populations and children as well as young adults remain understudied.^{281–285} Costs of productivity losses (i.e. the costs occurring when the productivity of individuals is affected by illness, treatment, disability or premature death) for instance, may be relevant to patients that already were (economically) productive before the onset of the disease.²⁸⁶ In the

case of most paediatric ALL patients, this is however not the case. Instead, patients' parents or caregivers face these losses. Since Dutch-specific data were unavailable concerning the productivity losses of parents and informal care, we made assumptions based upon available information in the literature.

For economic evaluations conducted from a US or Dutch perspective, it is recommended to consider future medical costs.^{42,287} While the US guidelines recommend the inclusion future non-medical (consumption) costs as well, the Dutch guideline does not mention its inclusion yet.^{42,287} Our study is the first to fully include both components in an evaluation of CAR-T cell therapy for pALL. Both aspects were added through the latest version of the iMTA PAID tool (version 3.0) which is available online (<https://imta.shinyapps.io/PAID3/>). The methodology of this tool is described elsewhere.^{259,260} Due to the favourable survival of patients with tisagenlecleucel, the discounted future costs of this treatment were extensive (i.e. 100,538 EUR), while these costs were significantly lower for Clo-M, Clo-C, or Blina (i.e. 18,371 EUR, 28,262 EUR, and 32,952 EUR, respectively). Long-term survivors of pALL may however not only induce costs in the future. Cured paediatric patients may be able to finish their school education and consequently join the workforce. We refer to these prospects as potential productivity gains, and made an attempt to quantify them in our analysis.

However, little is known about both educational and employment prospects of long-term survivors of childhood cancer. In addition, there is a lack of evidence and methodological guidance in how to integrate such gains in economic evaluations. Therefore, the inclusion of these cost savings in our model made use of rather simplistic assumptions and should be interpreted with caution. For instance, we assumed full and life-long employment of the modelled patients as from the age of 18 years. Future fluctuations on the job market or employment rates could not be reliably modelled and were beyond the scope of this research. Besides, it yet needs to be determined if patients in long-term EFS can or will start on the job market once they attain majority. It is apparent that patients who can potentially be cured from ALL may be enabled to finish their education and join the workforce in the future. However, the here modelled patients were all relapsed or refractory to previous treatment lines and non-attendance to school might have been significant during previous treatment lines. Research is needed to determine in how far the absence from school affects the job starting age and shapes future employment opportunities in this patient population. Furthermore, resulting from the uncertainty of the long-term effectiveness, no future productivity losses for the modelled patients were assumed that might result from long-term, disease-related absenteeism. Nevertheless, our approach may be seen as an illustration of the magnitude of potential economic gains resulting from improved survival, especially in pediatric diseases. Further research could quantify the potential productivity gains by elucidating how this aspect can be captured and integrated into cost-effectiveness analyses in a sound methodological manner.

Although this study is not the first to estimate the cost-effectiveness of tisagenlecleucel, it is the first to adopt a full societal perspective. Following a ‘mock appraisal’ commissioned by the UK National Institute for Health and Care Excellence (NICE) to assess whether changes to its methods and processes were needed,³⁸ several cost-effectiveness analyses were published in the US and Canada. Two studies had considered societal aspects in a scenario analysis, but none of them had considered productivity losses of caregivers, travel and hotel costs for patients and caregivers, informal care costs, and future medical costs including consumption costs altogether.^{254,256} In addition, input parameters and outcomes of the societal perspective were either not reported,²⁵⁶ or not clearly defined and point to evidence of adult patients, while paediatric patients are studied (see patient time in Sarkar et al.(2018)).²⁵⁴

When comparing our results to the other cost-effectiveness studies we found some disparities. Differences in incremental costs were highest between our study and Sarkar et al.²⁵⁴ for Clo-C, followed by costs for Clo-M when compared to the NICE mock appraisal.³⁸ The reason for these discrepancies can be explained by major differences in several cost input parameters. For instance, costs for tisagenlecleucel are higher in the US when compared to the Netherlands (475,000 USD [426,000 EUR] versus 320,000 EUR). Similarly, the NICE mock appraisal assumed even higher one-off costs for tisagenlecleucel of 528,600 GBP (587,697 EUR) per patient.³⁸ In addition, estimated costs for HSCT in all US studies were significantly higher when compared to our study. Sarkar et al.²⁵⁴ assumed HSCT costs ranging between 299,987 USD (267,456 EUR) for successful HSCT and 459,682 USD (409,834 EUR) for failed HSCT. Lin et al.²⁵⁵ estimated the HSCT costs to be 555,000 USD (483,904 EUR), which was similar to the estimates of Whittington et al.²⁵⁷ (560,000 USD [488,264 EUR]). For every modelled patient that received subsequent HSCT, our model considered one-time costs of 217,590 EUR per HSCT³¹ and no distinction was made between successful or failed treatment.

With the exception for Whittington et al.²⁵⁷, incremental effects in LYs could be regarded as similar between all studies. Incremental QALYs differed to a greater extent and were highest for the study of Lin et al.²⁵⁵ We hypothesize that this is mainly due to the use of different utility estimates. Lin et al.²⁵⁵ used a variety of utility estimates ranging between 0.56 to 0.92, depending on the health state or time. Our utility estimates were based on the ELIANA trial and ranged between 0.68 and 0.83, depending on the health states. Although we accounted for disutilities during any treatment, the stay at an intensive care unit, and graft-versus host disease, our utilities were consistently higher when compared to Lin et al.²⁵⁵

Finally, the divergent ICERs per QALY between the studies are a result of the difference in both costs and outcomes as explained above. Despite the several assumptions made in this study, we conclude that our results are robust (as tested through several sensitivity and scenario analyses) and that the conclusion of tisagenlecleucel being cost-effective is in line with all other cost-effectiveness studies for paediatric patients with r/r ALL. Furthermore, total costs from a societal perspective were higher for each treatment option when compared

to costs from a healthcare perspective. Although the increase in these costs was higher for tisagenlecleucel when compared to Clo-M, Clo-C, or Blina, none of the ICERs exceeded the WTP threshold of 80,000 EUR per QALY gained.

Chapter 6

Cost-effectiveness of lenalidomide plus rituximab versus rituximab monotherapy in patients with previously treated follicular lymphoma. A societal view.

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ABSTRACT

Introduction: Efficacy of lenalidomide plus rituximab (R-LEN) compared to rituximab monotherapy (R-mono) for patients with previously treated follicular lymphoma (FL) was investigated in AUGMENT (NCT01938001). Our aim was to evaluate the cost-effectiveness of R-LEN versus R-mono in this setting from a Dutch perspective.

Methods: Cost-effectiveness was assessed through a partitioned survival model with three health states from three perspectives (i.e. societal, healthcare and societal including future non-medical costs). Patient-level data from AUGMENT informed effectiveness parameters (i.e. long-term survival) and health state utilities. Resource use and prices were based on AUGMENT and the literature. Clinical experts validated efficacy input parameters and results. Uncertainty was explored through sensitivity and scenario analyses.

Results: R-LEN resulted in 1.7 incremental discounted QALYs. Total incremental discounted costs were 67,161 EUR from a societal perspective, resulting in an incremental cost-effectiveness ratio (ICER) of 40,493 EUR/QALY (healthcare: 37,951 EUR/QALY; societal including future non-medical costs: 49,296 EUR/QALY). Sensitivity analyses indicated some uncertainty in the model results. In some scenarios R-LEN exceed an ICER of 50,000 EUR/QALY.

Conclusion: R-LEN was cost-effective at a willingness-to-pay (WTP) threshold of 50,000 EUR/QALY in the base-case analyses. Scenario and sensitivity analyses indicated some level of uncertainty regarding this conclusion, depending on the chosen WTP-threshold and perspective.

INTRODUCTION

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL) in Western Europe and the United States, comprising over 35% of all NHLs and 70% of indolent lymphomas.²⁸⁸ In the Netherlands, the age-adjusted incidence rate for FL was 2.5 per 100,000 in 2016.²⁸⁹

Currently, several treatment options are available for patients who are refractory or relapsed from first-line therapy, none of which are considered curative.²⁹⁰ For these patients, rituximab,²⁹¹ interferon alfa-2b as an add-on to anticancer treatment,²⁹² ibrutinomab tiuxetan,²⁹³ obinutuzumab in combination with bendamustine,²⁹⁴ and idelalisib²⁹⁵ were the only approved treatment options by the European Medicines Agency (EMA) until recently. In December 2019, the EMA approved an extension of indication for the immunomodulatory drug lenalidomide.²⁹⁶ Lenalidomide in combination with rituximab (R-LEN) is since then authorized for adult patients with previously treated FL (Grade 1 – 3a) in Europe.

The EMA's decision was based on clinical evidence from the recently published phase III AUGMENT study, comparing R-LEN to rituximab plus placebo (R-mono) in previously treated patients with indolent FL or marginal zone lymphoma (MZL).²⁹⁷ In AUGMENT, R-LEN demonstrated statistically significant superiority in overall survival (OS) and progression-free survival (PFS) over the comparator regimen in the FL subgroup. OS probability at two years, assessed by the independent review committee (IRC) was 95% (95% CI, 90 to 98) for R-LEN and 86% (95% CI, 79 to 91) for R-mono.²⁹⁷ In addition, R-LEN was found to increase median PFS by approximately 25 months when compared to R-mono (hazard ratio, 0.40; 95% CI, 0.29 to 0.56; $P < .001$).²⁹⁷ The study also collected health-related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the 3-level classification system of the EQ-5D questionnaire (EQ-5D-3L).^{298,299} Preliminary results of these data suggest no negative impact of R-LEN on patients' HRQoL when compared to R-mono.³⁰⁰

While lenalidomide underwent central approval by the EMA, each European member state handles its own reimbursement procedure. In addition to considerations on the safety and efficacy of a new treatment, its cost-effectiveness is a key aspect when making both treatment and reimbursement decisions.³⁰¹ Especially when drug prices are relatively high, economic evaluations can provide the necessary information to make informed decisions. Such assessments combine several sources of evidence (i.e. efficacy and costs) to derive conclusions on the cost-effectiveness of a treatment.^{19,216} Analyses that also consider patients' HRQoL are commonly referred to as cost-utility analyses (CUAs). Currently, there is no evidence available on the cost-utility of R-LEN from a societal perspective in a European country.

Therefore, the aim of this study was to evaluate the cost-effectiveness of R-LEN when compared to R-mono in patients with previously treated FL in the Netherlands from a societal perspective. As suggested in the literature, we also present results from a healthcare perspective.³⁰² While future non-medical costs should be considered when performing CUAs from a societal perspective, not all pharmacoeconomic guidelines explicitly mention their inclusion yet.^{26,303,304} Consequently, the impact of these costs on the results of CUAs remains understudied.²⁶ For this study, future non-medical costs were considered for a third perspective to fill this gap.^{259,260,276}

METHODS

Patient-level data to inform model efficacy parameters were based on the AUGMENT FL subgroup. A detailed description of the methods can be found in online Appendix 6A.

We modelled a hypothetical cohort of patients by means of a partitioned survival model.³⁰⁵ This methodology is commonly used in decision modelling of new interventions in advanced cancers.³⁰⁵ Our analysis follows the recommendations of the Dutch guideline for conducting economic evaluations in health care (Dutch EE guideline).¹⁷⁴

The model comprised three states: progression free (PF), progressive disease (PD), and death. The simulation starts with administering either treatment option (R-LEN or R-mono) in the PF state. Simulated patients responding to treatment remained in the PF state and follow-up resource use was considered. In case patients relapsed or were refractory to R-LEN or R-mono, they were assumed to be in the PD state. Modelled patients could die at all times. Figure 1 schematically represents how patients can move through the model over time.

To determine the proportion of patients in each model state, we independently fit a range of parametric models to both PFS and OS in AUGMENT.³⁰⁶ Consequently, short-term

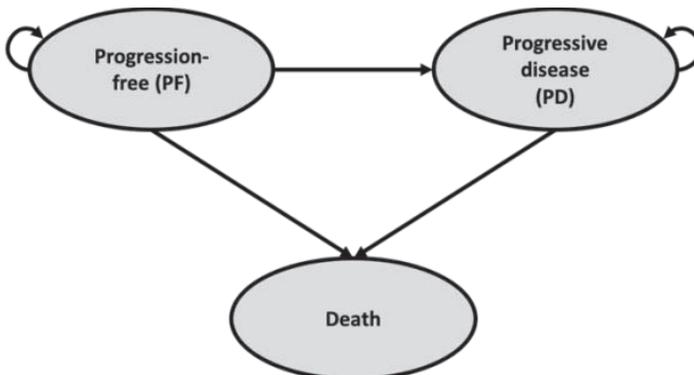


Figure 1 - Schematic representation of the de novo model

empirical data was extrapolated to a lifetime horizon. The model was adjusted for general population mortality (i.e. extrapolated survival could not exceed this mortality) and a finite treatment effect for R-LEN was assumed (i.e. five years, based on clinical expert opinion). Effects were discounted with 1.5%.¹⁷⁴

The societal perspective of the base-case analysis included healthcare costs for drugs (acquisition and administration), adverse events (AEs), subsequent treatment, and future medical costs. Prices for drug acquisition were taken from the Dutch drug database (April 2020),⁵¹ and drug administration costs were based on a micro-costing study on intravenous rituximab administration in the Netherlands.²⁷⁵ The model considered grade 3-4 AEs with more than 5% occurrence as observed in AUGMENT.²⁹⁷ AE costs and disutilities were based on the literature.³⁰⁷⁻³⁰⁹ Subsequent treatment during PD and resource use during all follow-up visits were based on the Dutch clinical practice guideline (CPG) for FL.³¹⁰ Prices for these items were taken from the Dutch costing manual.³¹¹

Additionally, societal costs for travel, productivity losses, and informal care were considered in the model base-case (see online Appendix 6A for more detail). Future non-medical costs were included using the iMTA PAID tool (version 3.0).^{259,260,276}

All costs are expressed in 2019 Euros and both prices and costs of earlier years were indexed to 2019 with the pertinent consumer price index.³¹² Costs were discounted with 4%.¹⁷⁴

Effect outcomes include total average life years (LYs) as well as quality-adjusted life years (QALYs) per patient and were validated by clinical experts.

Furthermore, we report total incremental costs and effects as well as the incremental cost-effectiveness ratio (ICER) of R-LEN when compared to R-mono. To determine whether R-LEN is cost-effective the applicable willingness-to-pay (WTP) threshold was estimated using the Burden-of-Disease calculator.³¹³

We conducted several scenario analyses with varying efficacy, utility, and cost parameters. Also we tested different assumptions of the treatment effect duration (see online Appendix 6A). Uncertainty of the model input parameters and estimates was assessed through deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA).

An overview of all parameter (mean) values, their standard error (SE), assumed distributions as well as lower and upper bounds are summarized in Table 1.

Table 1 - Overview of model input parameters

Type	Parameter	Base case value	SE	Distribution	Lower bound	Upper bound	Source	Remark
Model setting	% discount rate: costs	4.0	NA	NA	NA	NA	Dutch EE guideline ³¹⁴	None
	% discount rate: effects	1.5	NA	NA	NA	NA	Dutch EE guideline ³¹⁴	None
Patient characteristics	Age, years (mean)	61.18	0.65	Normal	59.89	62.45	AUGMENT study ²⁹⁷	None
	BSA (mean)	1.85	0.01	Normal	1.82	1.88	AUGMENT study IPD ²⁹⁷	None
Resource use	% female patients	52	NA	Beta	46	58	AUGMENT study IPD ²⁹⁷	None
	AE %: neutropenia in R-LEN	0.5	NA	Beta	0.42	0.58	AUGEMENT study IPD ²⁹⁷	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
Resource use	AE %: leukopenia in R-LEN	0.07	NA	Beta	0.03	0.11	AUGEMENT study IPD ²⁹⁷	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
	AE %: anemia in R-LEN	0.05	NA	Beta	0.02	0.09	AUGEMENT study IPD ²⁹⁷	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
Resource use	AE %: neutropenia in R-mono	0.12	NA	Beta	0.07	0.18	AUGEMENT study IPD ²⁹⁷	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).

Table 1 - Overview of model input parameters (*continued*)

Type	Parameter	Base case value	SE	Distribution	Lower bound	Upper bound	Source	Remark
	AE %: leukopenia in R-mono	0.02	NA	Beta	0	0.05	AUGEMENT study IPD ³⁹⁷	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
	AE %: anemia in R-mono	0.01	NA	Beta	0	0.02	AUGEMENT study IPD ³⁹⁷	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
	Informal care: probability of receiving (in %)	22	5	Gamma	0	60	iMTA iCARE tool based on HRQoL data in AUGMENT	Upper bound probability was based on Doorduijn et al. (2004) ²⁷⁹
	Informal care time when receiving (hours per week)	16.00	0.81	Gamma	15.11	18.28	iMTA iCARE tool based on HRQoL data in AUGMENT	None
	Patients returning back to work after first-line therapy (in %)	50	5	Beta	40	60	Arboe et al. ³¹⁵	None
Prices	Drug acquisition: lenalidomide 2.5 mg	226.21	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 5 mg	232.54	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 7.5 mg	238.87	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 10 mg	241.16	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 15 mg	248.99	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses

Table 1 - Overview of model input parameters (*continued*)

Type	Parameter	Base case value	SE	Distribution	Lower bound	Upper bound	Source	Remark
	Drug acquisition: lenalidomide 20 mg	259.18	NA	NA	NA	NA	NA G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 25 mg	265.12	NA	NA	NA	NA	NA G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: rituximab 100 mg (i.v.)	227.46	NA	NA	NA	NA	NA G-standaard via Z-index	None
	Drug acquisition: rituximab 500 mg (i.v.)	1,137.32	NA	NA	NA	NA	NA G-standaard via Z-index	None
	Drug acquisition: rituximab 1400 mg (s.c.)	1,680.71	NA	NA	NA	NA	NA G-standaard via Z-index	None
	Physician specialist (per consultation)	120.64	12.06	Gamma	98.16	145.41	Dutch EE guideline ³¹⁴	None
	Follow-up price: CT	188.3	18.83	Gamma	153.21	226.96	Dutch EE guideline ³¹⁴	None
	Follow-up price: Outpatient clinic	140.92	14.09	Gamma	114.66	169.85	Dutch EE guideline ³¹⁴	None
	Imaging price: abdominal ultrasound	120.9	12.09	Gamma	98.37	145.72	Dutch EE guideline ³¹⁴	None
	Lab price: TSH	4.77	0.48	Gamma	3.88	5.75	Dutch EE guideline ³¹⁴	None
	Lab price: LDH	1.81	0.18	Gamma	1.47	2.18	Dutch EE guideline ³¹⁴	None
	Lab price: WBC	1.80	0.18	Gamma	1.46	2.17	Dutch EE guideline ³¹⁴	None
	Lab price: platelets	1.78	0.18	Gamma	1.45	2.15	Dutch EE guideline ³¹⁴	None
	Lab price: hemoglobin	1.73	0.17	Gamma	1.41	2.09	Dutch EE guideline ³¹⁴	None
	Lab price: creatinine	1.64	0.16	Gamma	1.33	1.98	Dutch EE guideline ³¹⁴	None
	Informal care price (per hour)	14.95	1.5	Gamma	12.16	18.02	Dutch EE guideline ³¹⁴	None

Table 1 - Overview of model input parameters (*continued*)

Type	Parameter	Base case value	SE	Distribution	Lower bound	Upper bound	Source	Remark
	Productivity loss price (per hour)	37.08	3.71	Gamma	30.17	44.69	Dutch EE guideline ³¹⁴	None
Costs	Drug administration: i.v. therapy	167.82	12.6	Gamma	144.03	193.41	Franken et al. ²⁷⁵	None
	Drug administration: s.c. therapy	56.54	5.87	Gamma	45.63	68.6	Franken et al. ²⁷⁵	None
	Travel costs: for i.v. administration	33.39	3.34	Gamma	27.17	40.24	Franken et al. ²⁷⁵	None
	Travel costs: for s.c. administration	8.2	0.82	Gamma	6.67	9.88	Franken et al. ²⁷⁵	None
	AE costs: neutropenia	1171.24	530.82	Gamma	373.01	2417.96	Bouwmans et al. ³⁰⁷	None
	AE costs: leukopenia	1171.24	530.82	Gamma	373.01	2417.96	Bouwmans et al. ³⁰⁷	None
	AE costs: anemia	1595.38	479.52	Gamma	798.45	2663.5	Bouwmans et al. ³⁰⁷	None
Utilities and disutilities	Utility: PFS	0.854	0.01	Beta	0.754	0.954	AUGEMENT study IPD ²⁹⁷	None
	Utility: PD	0.854	0.01	Beta	0.754	0.954	AUGEMENT study IPD ²⁹⁷	None
	Disutility: neutropenia	0.090	0.02	Beta	0.059	0.120	Nafces et al. ³⁰⁸	None
	Disutility: leukopenia	0.090	0.02	Beta	0.059	0.120	Assumed to be the same as neutropenia	None
	Disutility: anemia	0.119	0.02	Beta	0.073	0.165	Swinburn et al. ³⁰⁹	None

AE = adverse event; BSA = Body surface area; CT = computerized tomography scan; EE = economic evaluation; HRQoL = health-related quality of life; IPD = individual patient data; i.v. = intravenous; LDH = lactate dehydrogenase; mg = milligram; NA = not applicable; PD = progressive disease; PFS = progression free survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy; s.c. = subcutaneous; SE = standard error; TSH = thyroid stimulating hormone; WBC = white blood cells

RESULTS

Efficacy

Based on the statistical goodness-of-fit criteria (see online Appendix 6B) and clinical expert opinion, we selected the Weibull and the log-normal distribution for the survival extrapolation of PFS and OS until year five, respectively. Thereafter, the hazard ratios between R-LEN and R-mono were kept constant both for PFS and OS extrapolations (see online Appendix 6A). For the R-LEN arm, the estimated probability of PFS at 5 and 10 years was 27% and 1%, respectively, in the R-LEN group. For patients receiving R-mono, these probabilities were 5% and 0%, meaning that all patients had progressed or died after 10 years. The estimated OS probabilities after R-LEN at 5, 10, 20, and 30 years amounted to 83%, 58%, 33% and 11%, respectively. After R-mono, these probabilities were 67%, 47%, 27%, and 9%, respectively. Empirical and modelled PFS and OS of both groups are depicted in Figures 2 and 3. The model estimated 12.9 LYs and 10.8 QALYs for R-LEN and 10.9 LYs and 9.1 QALYs for R-mono (discounted results).

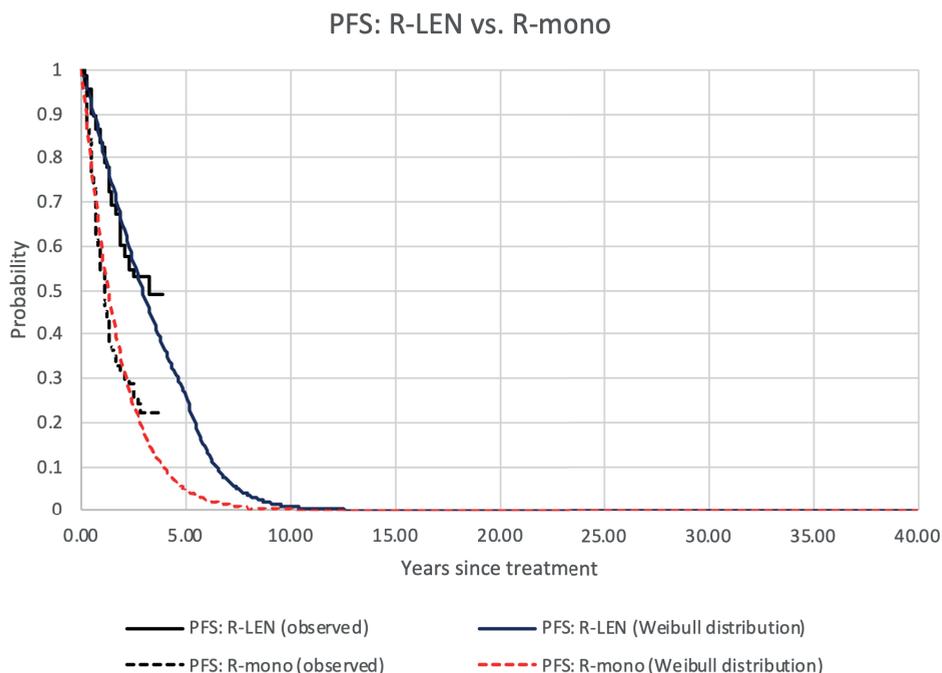


Figure 2 - Empirical and extrapolated PFS

PFS = progression-free survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy

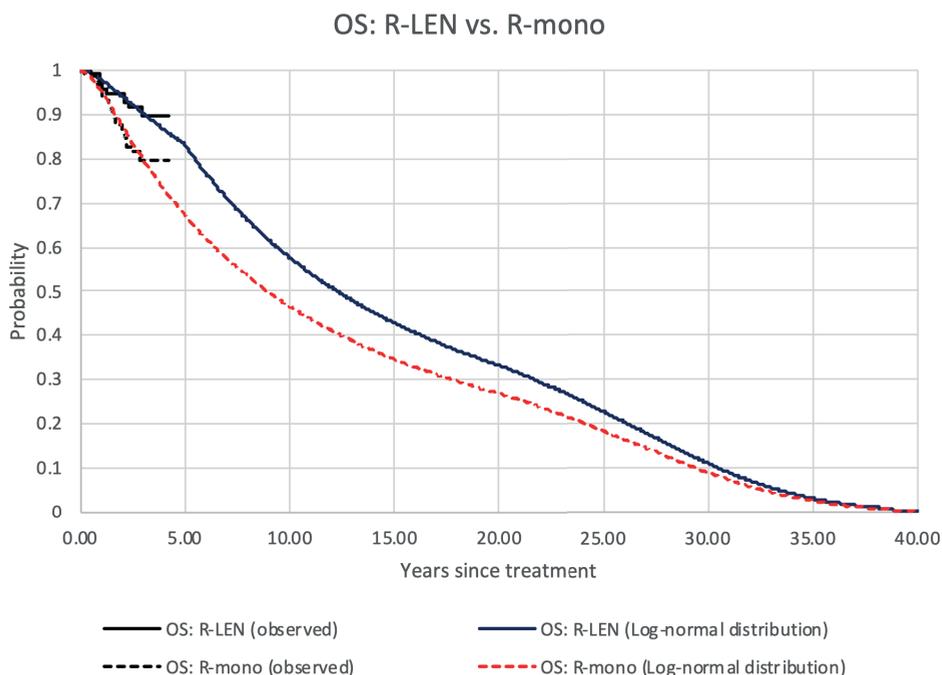


Figure 3 - Empirical and extrapolated OS

OS = overall survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy

Costs

The presented costs in Table 2 are average, discounted, lifetime costs per patient. Undiscounted costs can be found in online Appendix 6B.

Total costs from the base-case societal perspective were 200,355 EUR and 132,789 EUR for R-LEN and R-mono, respectively. Major cost drivers were future medical costs (R-LEN: 78,127 EUR; R-mono: 65,960 EUR), followed by drug acquisition costs for R-LEN (57,455 EUR), and informal care (R-LEN: 28,128 EUR; R-mono: 23,952 EUR). Total healthcare costs were 165,547 EUR and 102,233 EUR for R-LEN and R-mono, respectively. When future non-medical costs were considered in a societal perspective, total costs were 299,943 EUR and 217,687 EUR for R-LEN and R-mono, respectively.

Incremental cost-effectiveness ratio

Total incremental costs of R-LEN when compared to R-mono were 67,566 EUR from a societal perspective. Incremental costs were highest for drug acquisition (50,483 EUR), followed by incremental future medical costs (12,167 EUR). Only total costs for subsequent treatment regimens were lower for R-LEN when compared to R-mono. This was because modelled patients receiving R-LEN progressed later when compared to patients with R-

Table 2 - Model results: costs, effects and increments

Perspective	Costs in EUR										Effects	
	Drug acquisition	Drug administration	Adverse events	Subsequent treatment	Follow-up	Informal care	Productivity losses	Future medical (unrelated diseases)	Future non-medical	Total costs	Life years (PFS; PD)	QALYs (PFS; PD)
Societal												
R-LEN	57,455	1,096	743	19,990	8,692	28,128	6,123	78,127	NA	200,355	12.9 (3.2; 0)	10.8 (2.8; 8)
R-mono	6,972	692	176	21,240	7,677	23,952	6,119	65,960	NA	132,789	10.9 (1.7; 9.1)	9.1 (1.5; 7.6)
Increments	50,483	404	567	-1,250	1,015	4,176	4	12,167	NA	67,566	2 (1.5; 0.5)	1.7 (1.3; 0.4)
Healthcare												
R-LEN	57,455	957	743	19,805	8,459	NA	NA	78,127	NA	165,547	12.9 (3.2; 0)	10.8 (2.8; 8)
R-mono	6,972	592	176	21,043	7,479	NA	NA	65,960	NA	102,223	10.9 (1.7; 9.1)	9.1 (1.5; 7.6)
Increments	50,483	365	567	-1,238	980	NA	NA	12,167	NA	63,324	2 (1.5; 0.5)	1.7 (1.3; 0.4)
Societal incl. future non-medical consumption costs												
R-LEN	57,455	1,096	743	19,990	8,692	28,128	6,123	78,127	99,588	299,943	12.9 (3.2; 0)	10.8 (2.8; 8)
R-mono	6,972	692	176	21,240	7,677	23,952	6,119	65,960	84,899	217,687	10.9 (1.7; 9.1)	9.1 (1.5; 7.6)
Increments	50,483	404	567	-1,250	1,015	4,176	4	12,167	14,689	82,256	2 (1.5; 0.5)	1.7 (1.3; 0.4)

EUR = Euro (currency); PD = progressive disease; PFS = progression free survival; QALYs = quality-adjusted life years; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy

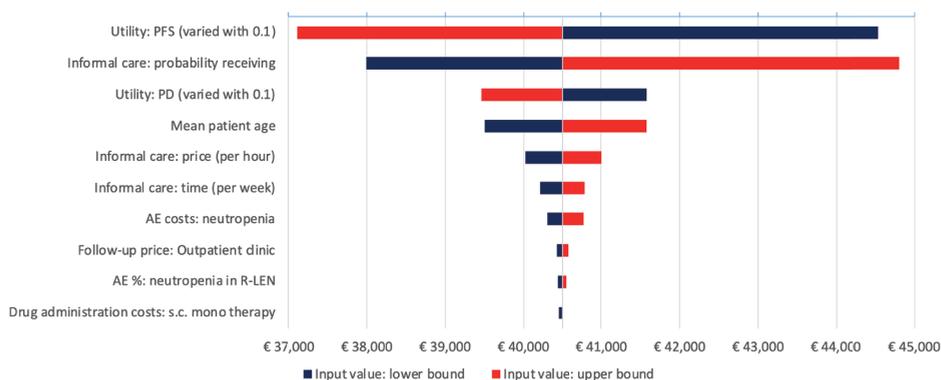


Figure 4 - Tornado diagram (societal perspective)

AE = adverse event; PD = progressive disease; PF = progression-free; R-LEN = rituximab plus lenalidomide

mono. Consequently, subsequent treatment is administered later and hence the effect of discounting these costs leads to lower costs.

The base-case ICER was 40,493 EUR/QALY (see Table 3). When considering healthcare costs only, the ICER was 37,951 EUR/QALY gained. When future non-medical costs were considered for a societal perspective the ICER increased to 49,296 EUR/QALY gained. In online Appendix 6B, the ICERs from the undiscounted analysis are presented.

Based on the disease burden calculator,³¹³ the most likely WTP-threshold was 50,000 EUR/QALY (51.6%) (see online Appendix 6B).

Table 3 - Incremental cost-effectiveness ratios

	Perspective		
	<i>Societal</i>	<i>Healthcare</i>	<i>Societal incl. future non-medical consumption costs</i>
Incremental costs (EUR) per LY gained	33,681	31,567	41,004
Incremental costs (EUR) per QALY gained	40,493	37,951	49,296

EUR = Euro (currency); LY = life years; QALY = quality-adjusted life year

Deterministic sensitivity analysis

The top ten influential parameters varied in the deterministic sensitivity analysis are summarized in Figure 4. Increasing the assumed utility value by 0.1 for progression-free disease resulted in the lowest ICER (i.e. 37,116 EUR/QALY), while assuming 60% of patients receiving informal care (instead of 22% in the base-case) resulted in the highest ICER (i.e. 44,816 EUR/QALY).

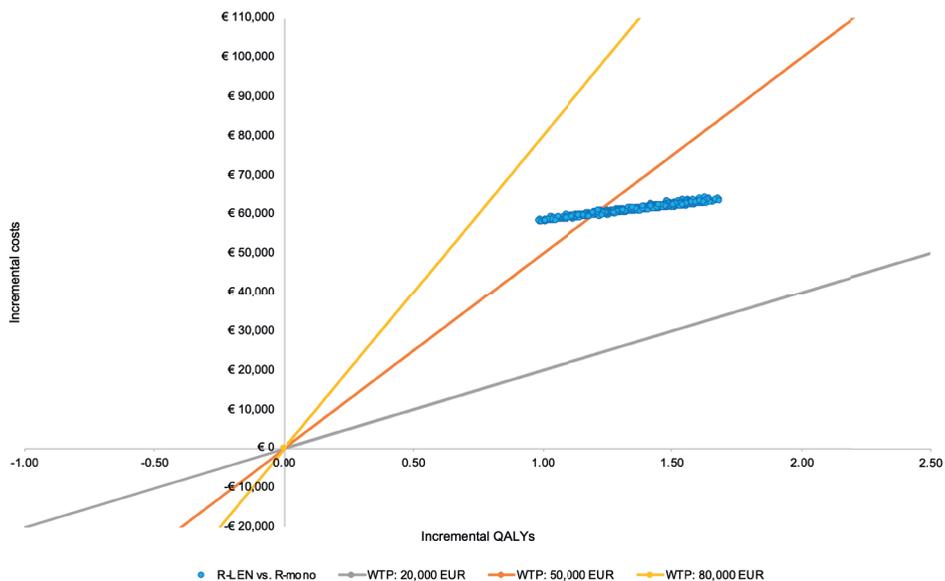


Figure 5 - Cost-effectiveness plane (societal perspective)

EUR = Euro (currency); QALYs = quality-adjusted life years; WTP = willingness-to-pay

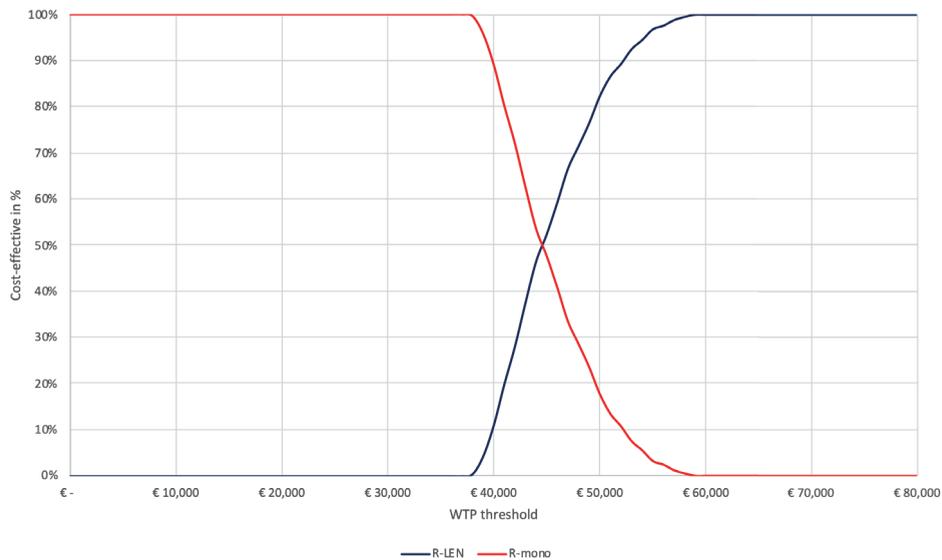


Figure 6 - Cost-effectiveness acceptability curve (societal perspective)

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis are presented in the cost-effectiveness plane (Figure 5) for the base-case societal perspective (see online Appendix 6B for all other perspectives). Assuming a WTP-threshold of 50,000 EUR/QALY gained, the probability of R-LEN being cost-effective was 67%. This probability was 82% when only healthcare costs were considered and 3% when future non-medical costs were included in the societal perspective. The cost-effectiveness acceptability curve in Figure 6 depicts a range of WTP-thresholds and the probability of R-LEN being cost-effective at each of those for the base-case societal perspective (see online Appendix 6B for all other perspectives).

Scenario analyses

From the base-case societal perspective, the following three scenarios exceeded the assumed WTP-threshold. First, assuming a treatment effect duration of three years yielded an ICER of 60,496 EUR/QALY gained. With an increase in the duration of the treatment effect, ICERs decreased to 33,354 EUR/QALY gained and 28,691 EUR/QALY gained after seven and ten years of treatment effect, respectively. Assuming no treatment effect waning resulted in the lowest ICER of all scenarios (25,114 EUR/QALY gained).

Second and third, selecting either the Gompertz or Weibull distribution to model OS of R-LEN and R-mono resulted in an ICER of 64,026 EUR/QALY and 53,040 EUR/QALY gained. The results of all scenario analyses can be found in online Appendix 6B.

DISCUSSION

Summary of Results

Our analyses show that R-LEN results in incremental LYs and QALYs gained when compared to R-mono. Simultaneously, R-LEN also results in higher costs when compared to R-mono, regardless of the chosen perspective. Deterministic ICERs of R-LEN versus R-mono ranged from 37,951 EUR/QALY (health care perspective) to 49,296 EUR/QALY gained (societal perspective including non-medical costs).

When is R-LEN cost-effective?

To determine whether R-LEN is cost-effective when compared to R-mono, the estimated ICERs need to be compared to the pertinent WTP-threshold. However, based on the disease burden calculator, two WTP-thresholds were nearly equally likely to be applicable. For this analysis we compared the respective ICER to a 50,000 EUR/QALY gained WTP-threshold as this had the highest probability of being applicable (see online Appendix 6B). At this WTP-threshold, R-LEN is cost-effective when compared to R-mono as all deterministic ICERs (i.e. from all perspectives) were below that threshold. However, PSA simulations

resulted in some variability in the modelled results (see Figure 5). The probability of R-LEN being cost-effective from a societal perspective started to increase from 0% at approximately 40,000 EUR/QALY gained to 100% at 62,000 EUR/QALY gained (see Figure 6).

Comparison with other studies

While this is the first cost-utility analysis of R-LEN for previously treated FL patients from a societal perspective, R-LEN has been evaluated in the same patient population from a UK healthcare perspective for a single technology appraisal to the NICE.³¹⁶ The NICE recommended R-LEN as a treatment option, stating an ICER of 20,156 GBP (approx. 22,976 EUR) per QALY gained when R-LEN was compared to R-CVP.³¹⁷ In the committee papers, an ICER of 17,233 GBP (approx. 19,644 EUR) per QALY gained can be found when R-LEN was compared to R-mono.³¹⁶ Although the modelled OS estimates between the NICE assessment and our study are comparable, the estimated ICERs deviate. This may be due to several reasons. First, the UK ICERs already include a confidential price discount of lenalidomide. Second, even without such a discount, the UK list price for lenalidomide is less than the Dutch list price. Furthermore, the UK analysis comparing R-LEN to R-mono used different parametric survival models and utility values when compared to our analysis.³¹⁶

Recently, another CUA was published by Zhang et al.³¹⁸ The study concluded that R-LEN is not cost-effective with an ICER of 49,849 EUR (58,812 USD) per QALY when compared to R-mono for r/r FL from a Chinese societal perspective. Several methodological aspects between this and our study exist that need to be addressed. First, Zhang et al. did not have patient level data available and therefore extracted survival data from the published Kaplan-Meier curves from the AUGMENT trial. This approach does not allow for stratification by diagnosis, and hence survival data of FL and MZL patients were used together to estimate long-term survival. Second, it was claimed that results were estimated on a lifetime horizon (i.e. until all patients had died). However, the actual time horizon used in the model was 10 years. Consequently, any costs or effects occurring after these 10 years were not captured. Third, Zhang et al. stated that costs were estimated from a societal perspective. Nevertheless, only direct medical costs were considered.

Assumptions on rituximab

Clinical experts mentioned that rituximab can be given s.c. when it is the only administered drug (as in R-mono) or when the combination drug is either administered s.c. or orally (as in R-LEN). Apart from being more time-efficient for both patients and health care staff, s.c. administration of rituximab in general leads to lower resource use and costs when compared to i.v. administration.²⁷⁵ Nevertheless, the experts indicated that rituximab is usually administered i.v. since the price of its biosimilar version is lower when compared to the reference product. In contrast to this, Dutch list prices for rituximab and its biosimilars do not differ. Eventual discounts are the result of confidential price negotiations between

individual hospitals and the manufacturer. To remain transparent, we adhered to the list prices for rituximab and assumed s.c. administration in both R-LEN and R-mono.

The assumption of s.c. versus i.v. administration for rituximab was tested in scenarios four and five (see online Appendix 6B) and did not lead to meaningful changes in the ICER. Assuming a lower price for rituximab (e.g. as a result of using a biosimilar) was not formally tested. However, a price discount for rituximab would affect both R-LEN and R-mono at the same extent and hence changes in the ICER are not expected.

Strength and weaknesses

In our model, incremental life years were determined by the choice of the parametric survival model to extrapolate empirical trial data and the assumption of the treatment effect waning. Ideally, long-term follow-up data would inform the distribution of patients in each health state (i.e. PF or PD). These data are however not available, and with limited follow-up time in AUGMENT (median= 28.3 months),²⁹⁷ extrapolation to a longer time horizon was necessary. Therefore, we fit several parametric survival models and consulted clinical experts to validate these long-term estimates.

Our sensitivity analyses show that the choice of a parametric survival function for OS can influence the decision whether R-LEN can be considered cost-effective at a WTP-threshold of 50,000 EUR/QALY gained. Both Gompertz and Weibull distribution resulted in an ICER above that threshold (i.e. 63,581 EUR/QALY and 52,685 EUR/QALY, respectively from a societal perspective). Empirical survival data with a longer follow-up period than in AUGMENT might lead to different results with less uncertainty.

Furthermore, the assumption on the treatment effect duration heavily impacted both the modelled effectiveness and the ICER. Assuming an infinite treatment effect duration for R-LEN resulted in the most favorable ICER of all scenario analyses from a societal perspective (24,983 EUR/QALY), while an effect duration of three years produced the least favorable ICER of 60,181 EUR/QALY gained. Which exact time point to assume for the treatment effect waning is a matter of ongoing discussion, but the NICE committee agreed that a five year horizon was appropriate (with clinical input suggesting a treatment effect lasting between 5 and 10 years).³¹⁶ Empirical OS and PFS data of AUGMENT indicate a benefit of R-LEN over R-mono.²⁹⁷ After trial follow-up there are several possibilities to extrapolate this treatment effect. It can be assumed to either further increase, remain constant, or decrease. Due to the immunomodulatory effect of lenalidomide we considered a constant treatment effect after five years post treatment to be a conservative estimate.

Another important aspect of determining the modelled effectiveness is the utility value for the different model health states (i.e. PF and PD). Based on the analyses of AUGMENT HRQoL data, we found no differences between either treatment option (i.e. R-LEN or R-mono) or health state (i.e. PFS or PD), which was in line with a previous analysis of the same data.³⁰⁰ No difference in HRQoL between health states seems counterintuitive. For

a scenario analysis, we therefore used the study by Wild et al. (2006) with utility values of 0.805 for PF and 0.736 for PD.³¹⁹ Although often used in economic evaluations, the reference is only available as a conference abstract with limited information on the methodology or utility values. However, neither the variation of utility values in the DSA nor the scenario with utility values of Wild et al.³¹⁹ exceeded an ICER of 50,000 EUR/QALY gained. Further research is needed to determine whether there is indeed no difference in HRQoL between patients who are PF or in PD.

The assumed average starting age of the modelled patient cohort showed to be an influential factor for the estimated ICER (see DSA results). While the mean age of FL patients in AUGMENT was approximately 61 years, clinical experts found this to be a rather young age for previously treated FL patients. Indeed, the median age at FL diagnosis for Dutch patients between 2014 and 2016 in the Netherlands was 64 years (range: 55 – 72, mean not reported).²⁸⁹ In the DSA, the influence of assuming different ages at treatment start found that age was indeed one of the most influential parameters for the model results. It needs to be noted that changing the assumed age at treatment start in the model does not lead to different outcomes of the parametric survival estimations. The variations in age mainly influence the remaining time in the model until the lifetime horizon is reached as well as the age-adjusted utility decrements. Only empirical data from a patient cohort with an older average age than in AUGMENT would lead to different outcomes in parametric survival estimations. Such data is however not available for R-LEN versus R-mono.

While we acknowledge the limited use of R-mono in (Dutch) clinical practice, there are currently no clinical data available from a phase III study comparing R-LEN to any other comparator than R-mono in previously treated FL patients. Nevertheless, the cost-effectiveness estimated for R-LEN compared to R-CHOP and R-CVP could be very relevant for clinical and reimbursement decisionmakers. For this purpose reliable evidence needs to be available, however. The modelled effectiveness of R-mono can be seen as a conservative estimate since both R-CHOP and R-CVP are generally considered to be more effective when compared to R-mono.³¹⁶ Nevertheless, results of the RELEVANCE trial comparing R-LEN to R-chemo in advanced untreated FL patients suggest similar efficacy results between these treatments.³²⁰ Whether this holds true for later treatment lines needs to be confirmed. Based on the Dutch CPG for FL,³¹⁰ total treatment costs of an R-CHOP or R-CVP regimen are approximately 3,000 EUR or 5,800 EUR more expensive than R-mono. It can be hypothesized that most other cost items of R-CHOP and R-CVP will be similar or higher when compared to R-mono. Consequently, a comparison of R-LEN to R-CHOP or R-CVP will lead to lower incremental total costs when compared to R-mono. In case effectiveness outcomes of R-CHOP or R-CVP are similar to R-mono, the ICER of R-LEN when compared to the former two treatment option will be lower than the ICER of this analysis. Real-world evidence, for instance from clinical registries, could shed light on the difference in effectiveness between R-mono and R-CHOP / R-CVP.

As of June 1, 2020 R-LEN is reimbursed under a confidential commercial agreement between the manufacturer and the Ministry of Health in the Netherlands.³²¹ Details of this confidential agreement (e.g. price discount on lenalidomide) are not taken into account for this evaluation. It can be assumed that a financial discount on the drug price of lenalidomide will result in a more favorable ICER compared to this analysis.

CONCLUSION

Our results show that R-LEN can be considered cost-effective at a WTP-threshold of 50,000 EUR/QALY gained from the base-case analysis. Nevertheless, this result is marked by some uncertainty. Long-term efficacy data could validate the model results and reduce this uncertainty. Although more recent and extensive data would be preferred, a further exploration of real-world evidence (e.g. from cancer registries) could be a first step.

PART III

**Implications of cost-utility
analyses of novel and expensive
treatments in haemato-oncology
on healthcare decision-making**

Chapter 7

Obinutuzumab in combination with chemotherapy for the first-line treatment of patients with advanced follicular lymphoma. An evidence review group evaluation of the NICE single technology appraisal

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ABSTRACT

Introduction: The National Institute for Health and Care Excellence (NICE), as part of the institute's single technology appraisal (STA) process, invited the company of obinutuzumab (Roche Products Limited) to submit evidence of the clinical and cost-effectiveness of the drug in combination with chemotherapy, with or without obinutuzumab as maintenance therapy for adult patients with untreated, advanced follicular lymphoma (FL) in the UK. Kleijnen Systematic Reviews Ltd (KSR), in collaboration with Erasmus University Rotterdam, was commissioned to act as the Evidence Review Group (ERG). This paper describes the company's submission, the ERG review, and NICE's subsequent decisions.

Methods: The clinical evidence was derived from two phase III, company-sponsored, randomised, open-label studies. Most evidence on obinutuzumab was based on the GALLIUM trial that compared obinutuzumab in combination with chemotherapy as induction followed by obinutuzumab maintenance monotherapy to rituximab in combination with chemotherapy as induction followed by rituximab maintenance monotherapy in previously untreated patients with FL (grades 1-3a). Long-term clinical evidence was based on the PRIMA trial, studying the benefit of two years of rituximab maintenance after first-line treatment in patients with FL. The cost-effectiveness evidence submitted by the company relied on a partitioned survival cost-utility model, implemented in Microsoft® Excel.

Results: The base case incremental cost-effectiveness ratio (ICER) presented in the company submission was below 20,000 GBP per quality-adjusted life-year (QALY) gained. Although the ERG concluded that the economic model met the NICE reference case to a reasonable extent, some errors were identified and several assumptions made by the company were challenged. A new base case scenario produced by the ERG suggested an ICER that was higher than the company base case, but still below £30,000 per QALY gained. However, some ERG scenario analyses were close to or even above the threshold. This was the case in particular for assuming a treatment effect that did not extend beyond trial follow-up.

Discussion: These results lead to an initial negative recommendation by the appraisal committee. Subsequently, the company submitted a revised base case focusing on patients at intermediate or high risk of premature mortality. Simultaneously, a further price discount for obinutuzumab was granted. In addition to the company's revised base case, the ERG suggested a restriction of the treatment effect to five years and implemented biosimilar uptake and cheaper prices for rituximab. All of these adjustments did not exceed £30,000 per QALY gained and therefore the use of obinutuzumab for patients with advanced FL and a FLIPI score of two or more could be recommended.

INTRODUCTION

Within the United Kingdom (UK) National Health Service (NHS), the National Institute for Health and Care Excellence (NICE) may recommend the use of new and existing medicines and treatments through single technology appraisals (STAs).³²² During such appraisals, the NICE Appraisal Committee (AC) reviews clinical and economic evidence on the technology under investigation based on the company submission (CS) taking into account the critique of a report from an appointed independent Evidence Review Group (ERG) as well as advice from other consultees (e.g. patients, experts and other stakeholders). After consideration of all the relevant evidence, the AC formulates preliminary guidance in the form of the Appraisal Consultation Document (ACD) as to whether or not to recommend the technology. The stakeholders are invited to comment on this ACD and the submitted evidence. A subsequent ACD may be produced or a Final Appraisal Determination (FAD) is issued. Once recommended by NICE, the NHS is legally obliged to fund and resource the appraised technology so that the patients' right to access these technologies is ensured.³²² This paper presents a summary of the ERG report and the development of the NICE guidance based on the AC's findings for the STA of obinutuzumab in combination with chemotherapy as an induction therapy followed by obinutuzumab maintenance monotherapy, for the first-line treatment of patients with advanced follicular lymphoma. Full details of all the relevant appraisal documents can be found on the NICE website (TA513).³²³

THE DECISION PROBLEM

Arising from lymphocytes, lymphomas are a heterogeneous group of malignancies of which about 90% are diagnosed as non-Hodgkin lymphomas (NHL).³²⁴ In the UK, NHL are the sixth most common type of cancer.³²⁵ With an annual incidence rate of 3.2 per 100,000, follicular lymphomas (FL) constitute the third most common subtype of NHL in UK.³²⁵ The median age at diagnosis for FL in the UK is about 65 years with a five-year relative survival rate of 86.5%.^{326,327} Survival of patients with FL can be predicted with either the Follicular Lymphoma International Predictive Index (FLIPI),³²⁸ or its revised version, known as FLIPI2.³²⁹ The FLIPI comprises a set of five predictive parameters (age, Ann Arbor stage, haemoglobin, serum LDH level, and number of nodal sites), discriminating patients into three risk groups (low, intermediate and high).³²⁸ FLIPI2 builds on five parameters as well, but only haemoglobin and age are shared with the FLIPI (β 2-microglobulin, longest diameter of the largest involved node, and bone marrow involvement are the other three).³²⁹ The lower the FLIPI/FLIPI2 score, the better the prognosis as well as overall survival (for FLIPI) and progression free survival (for FLIPI2) of patients with FL. A FLIPI score of 0 to 1 is regarded as low risk while a score of 2 or above signifies intermediate to high risk.

Due to the indolent nature of the disease, most patients present with advanced stages at first diagnosis and therefore require systemic treatment.^{326,330}

In the UK, patients with advanced, symptomatic FL, receive rituximab-containing treatment regimens as first-line therapy options, followed by two years maintenance therapy. However, despite receiving immunochemotherapy, an estimated 20% of patients with FL experience disease progression within two years from diagnosis.³³¹ Treatment for patients with advanced stage targets to control the disease, which is typified by a chronic course comprised of repeated relapses, treatment and progression.

As a Type II anti-CD20 antibody, obinutuzumab received marketing authorisation from the European Medicine Agency (EMA) for previously untreated chronic lymphocytic leukaemia (CLL) in July 2014.³³² In April 2016 and July 2017, the EMA extended the indication for obinutuzumab to FL.^{333,334} The scope for this STA set by NICE was to assess the use of obinutuzumab in combination with chemotherapy, with or without obinutuzumab as maintenance therapy (obin-chemo+obin) for people with untreated advanced FL in the UK. Mentioned comparators were rituximab monotherapy (although there was no marketing authorisation in the UK for this indication at time of appraisal), rituximab-based chemotherapy, with or without rituximab maintenance treatment, and bendamustine monotherapy (no marketing authorisation in the UK at the time of appraisal).

THE INDEPENDENT EVIDENCE REVIEW GROUP (ERG) REVIEW

Kleijnen Systematic Reviews Ltd (KSR), in collaboration with the Erasmus University Rotterdam constituted as the ERG and reviewed the evidence on the clinical and cost-effectiveness of obin-chemo+obin treatment for the first-line treatment of patients with advanced follicular lymphoma.

The ERG critically reviewed the evidence in the CS, the company's responses to clarification questions (RCQ) from the ERG, and the evidence provided after the publication of the ACD. Furthermore, the ERG explored the impact of assumptions on the incremental cost-effectiveness ratio (ICER), revised the economic model and explored additional scenario analyses.

Summary of the clinical evidence

The company conducted a systematic review to identify published and unpublished randomised clinical trial (RCT) evidence on the use obinutuzumab in previously untreated FL. Searches were carried out in June 2015 via PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). Update searches were reported for March and June 2017. At each time, separate supplementary searches of congress proceedings, clinical

trial registries, cancer association networks, and HTA agency websites were conducted to detect relevant unpublished and grey information. Ultimately, only one study was considered relevant to the decision problem. Therefore, the evidence on the efficacy of obinutuzumab was entirely based on GALLIUM, a phase III, open-label, multicentre RCT (BO21223, NCT01332968).³³⁵

GALLIUM was conducted at 177 trial centres in 18 countries with 21% of the participants (n=293) being from the UK. For this study, 1401 adult patients (≥18 years) with previously untreated, advanced iNHL were randomly assigned to two treatment arms. All analyses were based on the 1202 patients in the FL subpopulation, which included those with FLIPI scores from 0 upwards. One group received rituximab in combination with chemotherapy (R-chemo) as induction followed by rituximab (R) as maintenance. The other group received obinutuzumab in combination with chemotherapy (obin-chemo) as induction, followed by obinutuzumab (obin) as maintenance.

The primary outcome was investigator-assessed progression-free survival (INV-PFS). Secondary outcome measures included independent review committee-rated progression-free survival (IRC-PFS) and overall survival (IRC-OS), response rates at induction, maintenance and follow-up, adverse events (AEs), as well as health-related quality of life (HRQoL). The latter was assessed using the disease-specific Functional Assessment of Cancer Therapy for Patients with Lymphoma (FACT-Lym) instrument and the European Quality of Life (Euro-Qol) ED-5D-3L questionnaire.

Data reported in the CS were taken from the primary analysis of GALLIUM with a clinical cut-off in January 2016. Since the updated cut-off data were marked as academic in confidence, all data presented in this publication focus on the FL subpopulation at the January 2016 cut-off of the GALLIUM trial only.

The median age of the FL population in GALLIUM was 59 years (range: 23-88 years) with a female ratio of 53.2%. Of the three different chemotherapy regimens permitted, the most frequently used was bendamustine (57%), followed by CHOP (33%) and CVP (10%). Induction therapy was completed for 598 and 594 patients in the R-chemo and obin-chemo arm respectively. Subsequently, 527 patients in the R-chemo and 539 patients in the obin-chemo arm received maintenance therapy. These patients had achieved either a complete response (CR) or a partial response (PR) at this stage. Stable disease (SD) was achieved by 17 patients who therefore underwent observation. Patients in both maintenance and observation were followed clinically on a two-monthly basis for two years. A total of 341 patients in the R-chemo arm and 361 patients in the obin-chemo arm completed maintenance therapy. The reported overall median observation time was 34.4 months (range: 0.1–54.5 months) in the R-chemo arm and 34.8 months (range: 0.0–53.8 months) in the obin-chemo arm. The proportion of patients who had been observed for at least 2 and 3 years at the clinical cut-off was 87.7% and 44.1% in the R-chemo arm and 91.3% and 45.1% in the obin-chemo arm, respectively.

At the January 2016 cut-off, median INV-PFS as well as OS were not reached in both treatment arms. While the IRC-PFS was also not reached for the obin-chemo arm, it was reported with 51.2 (95% CI: 47.1 – not estimated) months for the R-chemo arm. Hazard ratios (HRs) comparing obin-chemo+obin to R-chemo+R were consistent and in favour for obin-chemo+obin in both INV-PFS (HR 0.66 [95% CI: 0.51, 0.85; $p = 0.0012$]) and IRC-PFS (0.71 [95% CI: 0.54, 0.93; $p = 0.0138$]). In the subgroup analyses, only low risk FLIPI scores showed a HR greater than 1.00 (HR 1.17 [95% CI: 0.63, 2.19]), while HRs of all other FLIPI scores ranged from 0.40-0.86.

Treatment-related AEs were observed in 94.8% of patients in the obin-chemo+obin arm and in 91.6% of patients in the R-chemo+R arm. Two System Organ Classes were more commonly observed ($\geq 10\%$) in the obin-chemo+obin arm when compared to the R-chemo+R: general disorders and administration site conditions (50.8% vs. 60.8%) as well as injury, poisoning and procedural complications (49.1% vs. 59.2%). In addition, a higher incidence of severe adverse event (SAEs) could be observed in the obin-chemo+obin arm than in the R-chemo+R arm (46.1% vs. 39.9%).

For both FACT-Lym questionnaire subscales and EQ-5D-3L scales, no notable differences between the treatment arms was detected at any time.

It is worthwhile mentioning that data for the late progressive disease states were taken from the PRIMA study, a phase III RCT of rituximab maintenance therapy in patients with high tumour burden FL that responded to rituximab plus chemotherapy induction. Characteristics of the PRIMA trial are reported elsewhere.^{336,337}

Critique and conclusion of the clinical evidence and interpretation

Regarding the systematic review, the ERG concluded that the population of the review was in line with the scope but the comparators were not. This was because the company had only included studies with a rituximab arm. As a deviation from the scope set by NICE, the company chose to consider only one comparator: rituximab in combination with chemotherapy, followed by rituximab maintenance treatment in patients achieving a response, which was criticised by the ERG. In addition, the ERG criticised that both data extraction and quality assessment of the studies retrieved by the literature search were not conducted by two reviewers independently. However, the ERG acknowledged that the GALLIUM trial was appropriate for the decision problem at hand due to its relevant population and reasonable proportion of UK patients (21%). The attention of the AC was drawn to the exclusion of grade 3B lymphoma in GALLIUM, which was found to be in line with the anticipated treatment with obinutuzumab. Although three different types of chemotherapy were offered in the trial, GALLIUM was not designed to investigate differences between these regimens. Therefore, the ERG could not decide whether the breakdown of regimens in the trial would reflect UK clinical practice. Due to GALLIUM being an open-label trial, the ERG concluded that the results of the IRC would be less prone to bias than the investigator

results. Furthermore, although the follow-up duration of the trial was reasonable, data were judged not fully mature for the main outcomes.

In its clarification response the company acknowledged that the GALLIUM cohort might on average be younger than the average UK patient population with FL which was confirmed by clinical experts consulted by the company and data of the Haematological Malignancy Research Network (HMRN)³³⁸ The ERG therefore adjusted the age at baseline in its own base case model.

Summary of the cost-effectiveness evidence

The company conducted several literature searches to detect studies on cost-effectiveness, health effects, as well as on cost and healthcare resource use. For the cost-effectiveness search, none of the retrieved references were considered relevant. Therefore, the company conducted a *de novo* economic evaluation of obinutuzumab in combination with chemotherapy compared with rituximab in combination with chemotherapy for the first-line treatment of patients with advanced FL.

For this purpose, the company developed an Excel-based five-state cohort transition Markov model with following health states: two progression-free survival (PFS) states for on and off treatment, two progressed disease states (PD) for early and late PD, and death. All simulated observations start in the PFS health state on treatment (obin-chemo+obin or R-chemo+R). Only patients responding to induction received maintenance (as per licence indication), which was only offered until progression or for a maximum of two years. Patients are considered 'off-treatment', when they complete or discontinue treatment in the PFS state. From the latter state, patients can remain in either PFS (on- or off-treatment) or transition due to a progressive disease or death. It is assumed that the time to progression after initial treatment is predictive for post progression mortality and overall survival. In particular, patients progressing within the first two years of initial treatment have significantly worse survival outcomes than those who did not progress that early.^{331,339} To account for different outcomes and costs to the cohorts of patients who experience an early or a late progression, two progressed disease (PD) states were introduced. Once patients enter any of the two PD states, they can only remain in this state until death. The cumulative deaths from PFS and early as well as late PD states were used to calculate overall survival in the model. Survival estimates beyond the observed trial duration were extrapolated using several parametric functions. The population considered in the *de novo* analysis was equal to the GALLIUM cohort in terms of average age, body weight, height und Body Surface Area (BSA) (see Table 1).

The company argued that, based on the observed long-term follow-up in the PRIMA study and the expert opinion from clinical advisors, there was no evidence of a finite duration of treatment effect in treatments of FL (including obin-chemo+obin and R-chemo+R). However, for the base case analysis a treatment effect duration of 9.75 years was assumed,

Table 1 – Patient baseline characteristics used in the company’s de novo economic evaluation

Patient characteristic	Baseline value	Source
Age (years)	57.9	GALLIUM trial data ³³⁵
Body weight (kg)	75.7	
Height (cm)	168.3	
Calculated Body Surface Area (m ²)	1.86	

based on the PRIMA study. This assumption was tested in the sensitivity analysis for its robustness with a minimum and maximum assumed treatment effect duration of five years and an infinite time duration, respectively.

The transition probabilities between the different model states were estimated from parametric survival functions fitted to the relevant data for the time to treatment discontinuation (TTTD), PFS, and post progression survival (PPS). Considered distribution were: exponential, Weibull, log-logistic, log-normal, gamma, and Gompertz. Their goodness of fit to the GALLIUM data was assessed with both the Akaike/Bayesian Information criterion (AIC/BIC).

In the model, OS was calculated as the sum of the time spent in both PFS and the two PD health states (early and late). For the PFS and early PD mortality estimates, the company relied on the investigator assessed (INV) data of the GALLIUM trial. Since in GALLIUM no PPS events in late progression were observed, late PD mortality estimates were based on the PRIMA study.

For the CS base case model, long-term PFS and early PD were modelled with an exponential distribution. The monthly probability of transitioning from PFS to death was based on the UK age-specific all-cause mortality rate or the PFS death rates in GALLIUM (whichever occurred first). The same method was applied for the post progression survival probabilities; except that late PD mortality rates were estimated using data from the PRIMA trial (instead of GALLIUM). This was necessary because the GALLIUM data was premature.

HRQoL utilities for the PFS states were based on EQ-5D values collected in the GALLIUM trial. However, since long-term EQ-5D values from this trial were considered immature, the utility inputs for the progressed model states were based on utilities elicited in another study that had originally been commissioned by Roche.³⁴⁰ Health state related costs used in the model consisted of costs for medication (induction and maintenance), supportive care, subsequent treatment in PD, transportation, and adverse events. Relevant medication costs included those of obinutuzumab, bendamustine, CHOP, CVP, and rituximab. The latter were based on 2017 UK reference prices.^{341,342} No vial sharing was assumed.

For both costs and utilities, a 3.5% discount rate was applied. In addition, the company conducted a one-way deterministic sensitivity analysis, several scenario analyses and a probabilistic sensitivity analysis (PSA) to explore parametric and structural uncertainty.

In the RCQ, the initial 40-year time horizon of the model was set to 50 years, following the ERG's request.

In the final model submitted by the company, the base-case ICER (cost per quality-adjusted life-year [QALY] gained) was lower than 20,000 GBP, the threshold set by NICE being somewhere between 20,000 GBP and 30,000 GBP, depending on plausibility of the evidence.³⁴³ In addition, in the PSA results, it was observed that the ICER never reached this threshold. Scenario analyses revealed that different assumptions on the length of treatment effect (no finite duration versus five years), discount values (3.5% vs. 1.5%), and the choice of the parametric survival curve (exponential vs. Weibull) for the PFS states had with the highest impact of the ICER but did not exceed the NICE threshold. In general, all ICERs presented by the company (base case, PSA, and scenario) were below 30,000 GBP per QALY gained.

Critique of the Cost-Effectiveness Evidence and Interpretation

After assessing the company's submitted evidence and model, the ERG concluded that, although the cost-effectiveness searches were well documented and reproducible, there were concerns regarding inclusion of a Line of Treatment facet that was overly restrictive. Revised searches were provided during the clarification process, which retrieved additional references. Despite the revision of the strategies, errors in the Cochrane Library search syntax were still present. The additional studies identified were not found to be relevant for the decision problem and were not included.

The economic model met the NICE reference case to a reasonable extent. Nevertheless, the ERG found that deviations might have occurred in both measurement and valuation of HRQoL. Other deviations included the company's choice of the intervention and the comparator. In general, the model was in line with the company's formulated decision problem but only partially in line with the scope. While the intervention in the scope was described as "*obinutuzumab in combination with chemotherapy, with or without obinutuzumab maintenance therapy*",³⁴⁴ the company assessed the obinutuzumab induction therapy with obinutuzumab maintenance therapy only. Hence, the cost-effectiveness of obinutuzumab in combination with chemotherapy induction without maintenance therapy was not explored in the submission. In terms of comparators, the company focussed on rituximab in combination with chemotherapy but did not include other relevant comparators listed in the NICE scope (such as rituximab mono-therapy or bendamustine mono-therapy).

For the model structure, the ERG concluded that the one used in the CS was slightly different from other, commonly used partitioned survival models in oncology.^{345,346} The transitions between the health states were explicitly modelled, and in addition to other models, the company had also incorporated early and late PD states, which was seen by the ERG as a valid addition for modelling FL patients. With regards to the analysis and extrapolation of the survival data, the company had followed the guidance from the NICE Decision Support

Unit (DSU).³⁰⁶ Nevertheless, the ERG criticised the choice of the exponential distribution for the PFS survival probabilities. Although the company had argued that the exponential distribution would result in a more conservative estimate when compared to the log-logistics distribution, the ERG considered the Weibull distribution would represent an even better estimate with similar AIC and BIC values. This was because the Weibull distribution predicted a 10-year PFS probability of 30.2%, which was in line with clinical expert opinion suggesting that approximately 60-70% of patients relapse in the first 10 years after treatment.

Furthermore, due to few mortality events in the GALLIUM study, the company had based the transition probabilities from PFS to death on pooled estimates between the treatment arms. Consequently, the probability of dying in PFS was assumed equal for both treatment arms. Yet, the number of observed deaths between the treatment arms differed and showed higher mortality in the obinutuzumab arm (although not statistically significant). Therefore, the ERG recommended applying different transition probabilities per arm for both PFS and post progression survival (early and late PD).

Another point of criticism by the ERG was the assumption of a finite duration of the treatment effect on PFS, which was the main driver of the cost effectiveness results. This assumption was made solely on data from the PRIMA trial, as long-term data from GALLIUM was lacking. In the model base case of the CS, a 9.75-year treatment effect was assumed although the longest follow-up in the GALLIUM trial (at the time of the submission) was five years. Therefore, the ERG considered a finite treatment effect of five years as a more conservative approach to model the cost effectiveness.

Similar to the critique of the clinical evidence, the ERG criticised the used on INV-PFS data instead of the IRC-PFS data.

Additional Exploratory Analysis Conducted by the ERG

After careful consideration of all input parameter assumptions in the company's base case, the ERG defined a new base-case scenario, including multiple adjustments to the company's base-case economic model. The adjustments were categorised following the suggestions of Kaltenthaler et al.³⁴⁷:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Ultimately, the ERG corrected five errors, three violations, had four matters of judgement, and tested four alternative scenarios (see online Appendices 7A and 7B for a complete list of all items). The most influential adjustments to the company's base case model were: (1) choosing the IRC-PFS data together with a Weibull distribution for the PFS extrapola-

tion, (2) applying age dependant utility decrements, (3) increasing the population's age at baseline, and (4) considering different mortality rates per treatment arm.

The ERG revised base-case ICER did not exceed the 30,000 GBP threshold per QALY gained. Simultaneously, in more than 50% of the PSA results, obin-chemo+obin was cost-effective when compared to R-chemo+R at a 30,000 GBP per QALY-gained threshold. For all but one scenario analyses, the estimated ICER remained below the 30,000 GBP threshold per QALY. Only assuming a treatment effect duration of five years (scenario 1a) yielded an ICER above 30,000 GBP per QALY gained. Choosing different sources for utilities in PFS and PD had a substantial impact on the ICER but did not exceed the mentioned threshold.

Conclusion of the ERG Report

The ERG concluded that the GALLIUM trial is a good quality RCT even though a number of limitations were found. For instance, the breakdown of chemotherapy regimens (CHOP, CVP, and bendamustine) received in the trial may not reflect UK clinical practise. Likewise, the median age of included individuals in GALLIUM was not reflective of the UK FL population. In addition, although the trial had a reasonable follow-up, data were not fully mature for the main outcomes. Consequently, the ERG expressed major concerns regarding the implementation of the treatment effectiveness. More specifically, choosing a shorter duration of the treatment effect than in the CS was a major driver for bringing the ICER close, or even above the 30,000 GBP per QALY-gained threshold. Choosing either INV-PFS or IRC-PFS data had a substantial impact on the ICER as well, although none of two scenarios exceeded the mentioned threshold. Other remaining concerns were related to PFS probability distributions, and choosing the same mortality rate for both treatment arms. In addition, the ERG could not verify the source of the stated utility values for the PD states since they were referenced with an abstract that did not present any EQ-5D values.³⁴⁰

Nevertheless, the ERG preferred base-case analysis resulted in an ICER lower than the 30,000 GBP per QALY threshold. Although the ICER seemed to be robust to most structural changes explored by the ERG, the scenario analyses conducted by the ERG showed that with different choices for the treatment effect duration or the utilities for the PD health state, the ICER could exceed the 30,000 GBP per QALY threshold.

ERG research recommendations

Most notable, the cost-effectiveness analyses could benefit from long-term follow-up results from GALLIUM. The results could validate some of the key assumptions made in the model such as the extrapolation of the PFS parametric survival functions, the duration of the treatment effect and the early/late mortality in the progressed disease state. Different mortality assumptions in the progressed disease state would lead to different PFS/OS surrogacy implications, which might have substantial impacts on incremental results as elaborated in other first-line treatment submissions in oncology.³⁴⁸ In addition, a more recent and transparent

measure of utility values for the PD health state would increase both validity and reliability of the HRQoL estimates. Future research should include a comparison of obinutuzumab with different chemotherapy regimens such as CHOP, CVP, and bendamustine to generate more reliable estimates for direct treatment comparisons.

Key methodological issues

Three issues were expressed by the ERG.

First, the company's assumption of a finite duration of treatment effect on PFS was a major driver for the ICER. The treatment effect duration was implemented by setting the hazard ratio of the modelled intervention to the comparator to one (i.e. no difference in treatment effect), once the end of the treatment effect was assumed. Although, the ERG deemed the technical realisation of the limited treatment effect duration appropriate, some methodical concerns on its duration were expressed. The company had based its assumption on the PRIMA study, where no finite duration of treatment effects between rituximab maintenance treatment compared with 'observation only' could be observed until the longest follow-up period of 9.75 years. Likewise, the assumption of proportional hazards between intervention and comparator arm seemed to hold throughout the PRIMA study. This was backed by clinical advisors who had suggested that there is no evidence of finite treatment effect in FL treatments, and that this might hold true for the comparison of obin-chemo+obin versus R-chemo+R. The ERG by contrast doubted the generalisability from the PRIMA results and their transferability to GALLIUM. A visual inspection also suggested that the log-cumulative hazard plots for PFS from GALLIUM converged. Hence, the proportional hazards assumption most likely did not hold. Based on the available evidence, no robust estimate alternative for a treatment effect duration could be given. On these grounds, the ERG proposed a duration of five years for the treatment effect, as this also reflected the longest follow-up time of the GALLIUM study.

Second, due to the immaturity on the GALLIUM data, the company used PRIMA data to model the late PD health states. This combination of evidence was done without any kind of adjustments. However, since patient characteristics between the two studies might not be comparable, an unadjusted use of these data might bias the model estimates.

Third, the company's assumption of no biosimilar uptake for rituximab was deemed implausible.

NICE GUIDANCE

Key issues Considered by the Appraisal Committee

Regarding the clinical evidence, the AC concluded that the population of the GALLIUM trial would reflect people with advanced FL receiving treatment within the NHS to a reason-

able extent. However, the trial was judged to be underpowered to show a difference in OS. In addition, the presented trial data was considered highly immature. Consequently, the AC could not conclude whether obinutuzumab could prolong overall survival when compared to rituximab. Although it was acknowledged that obinutuzumab delays disease progression in the short term, there was still uncertainty about a long-term effect on progression-free survival. Furthermore, the AC concluded that obinutuzumab is associated with higher burden of adverse events when compared to rituximab. In terms of HRQoL, the AC regarded the difference in the EQ-5D scores between the GALLIUM trial arms as not statistically significant.

For the cost-effectiveness analysis, the AC considered several key issues.

First, it recognised substantial uncertainty in the evidence base and ICER in terms of the treatment effect duration, extrapolation of progression free survival, resource use and the immaturity of the clinical data. In addition, the company's assumption on the treatment effect duration was criticised.

Second, the AC doubted the company's assumption of a 0% uptake of biosimilars for rituximab and was aware of two biosimilar versions of rituximab that had a market authorisation. In addition, the AC was informed that the current uptake was increasing and at around 40%.

Due to the substantial uncertainty in the evidence base and ICER, the AC concluded that an acceptable ICER threshold would not lie towards the upper part of the 20,000 GBP to 30,000 GBP per QALY gained range specified in the NICE's guide to the methods of technology appraisal.³⁴³ Other factors that could substantiate a 30,000 GBP per QALY gained such as the innovative nature of obinutuzumab or special consideration as a 'life-extending treatment at the end of life' were ruled out as well.

Ultimately, the ERG updated its base case analysis incorporating the ACs findings. This yielded an expected increase in the ICER, rendering the intervention not cost-effective at the threshold of 30,000 GBP per QALY gained.

Preliminary Guidance (First Appraisal Consultation Document [ACD])

For the first ACD, NICE had considered the initial evidence submitted by the company, the testimony of professional groups and other stakeholders, as well as the ERG report. In September 2017, NICE's first ACD did not recommend obinutuzumab within its marketing authorisation for untreated advanced FL in adults. This recommendation was however not intended to affect patients that had already started treatment with obinutuzumab before the guidance was published. For these patients no change in funding arrangements would take place. A second appraisal committee meeting was planned for October 2017. Until then, all consultees had the possibility to react to the previously presented evidence.

Response to Preliminary Guidance (First ACD)

In reaction to the first ACD, the company provided an updated version of its model including alternative assumptions and a revised base case population. The company argued that, although the trial was not powered for individual FLIPI subgroups, an analysis focussing only on intermediate and high FLIPI subgroups would result in sufficient PFS events for the modelling task. This was in line with the EMA requirement to include a statement in the obinutuzumab Summary of Product Characteristics that the “[...] efficacy in FLIPI low risk (0-1) patients is currently inconclusive [...]”,³⁴⁹

With regard to the duration of treatment effect, the company retained its earlier argumentation and assumed an infinite duration of treatment effect for obinutuzumab. Furthermore, the new model assumed independent PFS extrapolations for high and intermediate FLIPI subgroups (thus using a non-proportional hazards assumption) and implemented vial sharing.

Biosimilar uptake for rituximab was not considered for the base case but in scenario analyses. The company had based this assumption on the recent availability of biosimilar rituximab, claiming that the branded product would currently constitute the majority of IV rituximab used.

This new analysis yielded an ICER below £20,000 per QALY gained, whereas scenarios considering different proportions of market shares and price reductions for biosimilar rituximab showed an ICER above £20,000 per QALY.

In reaction to the new company model, the ERG proposed a new (final) base case that assumed a treatment effect duration of five years, independent PFS extrapolations for high and intermediate FLIPI subgroups (thus using a non-proportional hazards assumption), no vial sharing, and a 65% update of biosimilar IV rituximab.

In the meanwhile, the company had also agreed on a new patient access scheme that would provide a further discount to the list price of obinutuzumab. The level of the discount is, however, commercial in confidence. The new ERG base case (including the new patient access scheme) yielded an ICER below £30,000 per QALY gained.

Final Appraisal Determination (FAD)

Due to the revised economic analyses focussing on higher-risk subgroups and a further discounted price for obinutuzumab and rituximab, the ICER was estimated to be below £30,000 per QALY gained. Hence, the AC issued new guidance. In March 2018, the FAD recommended obinutuzumab as an option for untreated advanced FL in adults, restricted to patients with a FLIPI score of 2 or more (as intended by the company’s revised model), provided that the company would grant the negotiated simple price discount in the revised patient access scheme. Just as in the ACD, the recommendation was not intended to affect patients that had already started treatment with obinutuzumab before the guidance was published. For these patients no change in funding arrangements would take place.

CONCLUSIONS

This STA demonstrates that even an ICER of below £20,000 per QALY gained, as in the first company submission, is no guarantee for a positive recommendation by NICE. In fact, a high degree of uncertainty in the evidence base of the cost-effectiveness model might lead to a negative decision by NICE, even when the ERG's base case is below the £30,000 per QALY gained threshold. Instead, NICE is also valuing the degree of uncertainty that, in this case, was expressed by some initial ERG scenarios yielding an ICER close to and above the £30,000 threshold.

For this submission, the AC's major concerns were on the degree of uncertainty of the various cost-effectiveness model input parameters, particularly the treatment effect duration. Although in this STA most of these parameters were based on an RCT, the immaturity of its results did not allow for robust estimates concerning the long-term effects of obinutuzumab on progression-free survival. Furthermore, the AC acknowledged both cheaper prices and higher uptake of rituximab biosimilars. This was based on the 2017-2019 prescribed services commissioning for quality and innovation (CQUIN), issued by NHS England, encouraging the use of biosimilar products to reduce the costs for medicines.³⁵⁰ Consequently, the AC had assumed that most commissioners in England would prefer to purchase cheaper biosimilar versions rather than branded drugs.

Narrowing down the treatment indication to patients with a FLIPI score of 2 or higher, as well as providing a further discount on the price for obinutuzumab could reduce the degree of decision uncertainty to the extent that the AC could issue a positive recommendation. This final decision deviates from the originally intended patient group proposed by the company (no FLIPI score thresholds). Hence, when considering the scope of the first CS, NICE adopted a 'restricted' or 'optimized' decision to provide access to obinutuzumab while concomitantly reducing the decision uncertainty.^{351,352}

Chapter 8

Health Economic Aspects of Chimeric Antigen Receptor T-Cell Therapies for Haematological Cancers. Present and Future

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ABSTRACT

Introduction: Since 2018, two chimeric antigen receptor (CAR) T-cell therapies received approval from the European Medicine Agency, with list prices around 320,000 EUR per treatment. These high prices raise concerns for patient access and the sustainability of health care systems. We aimed to estimate the costs and budget impact associated with CAR T-cell therapies for current and future indications in hematological cancers from 2019 – 2029.

Methods: We focused on the former EU-5 and the Netherlands. We conducted a review of list prices, health technology assessment reports, budget impact analysis dossiers, and published cost-effectiveness analyses. We forecasted the ten-year health expenditures on CAR T-cells for several hematological cancers in selected EU countries.

Results: Nine cost-effectiveness studies were identified and list prices for CAR T-cell therapies ranged between 307,200 EUR and 350,000 EUR. Estimated additional costs for pre- and post-treatment were 50,359 EUR per patient, while the incremental costs of CAR T-cell therapy (when compared to care as usual) ranged between 276,086 EUR and 328,727 EUR. We estimated market entry of CAR T-cell therapies for chronic mantle cell lymphoma (MCL), follicular lymphoma (FL), lymphocytic leukemia (CLL), multiple myeloma (MM), and acute myeloid leukemia (AML) in 2021, 2022, 2022, 2022, and 2025, respectively. Cumulative expenditure estimates for existing and future indications from 2019 – 2029 were on average 28.5 billion EUR, 32.8 billion EUR, and 28.9 billion EUR when considering CAR T-cell therapy costs only, CAR T-cell therapy costs including pre- and post-treatment, and incremental CAR T-cell therapy costs, respectively.

Discussion: CAR T-cell therapies seem to be promising treatment options for hematological cancers but the financial burden on health care systems in the former EU-5 and the Netherlands will contribute to a substantial rise in health care expenditure in the field of hematology.

INTRODUCTION

It took almost 40 years from the time chimeric antigen receptor (CAR) T-cell therapy was first described in the 1980s to the approval of tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2017 and 2018, respectively.³⁵³ Thus far, the EMA approved tisagenlecleucel for the treatment of pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that are refractory, in relapse post-transplant or in second or later relapse as well as for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Axicabtagene ciloleucel is currently approved by the EMA for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. Both therapies are autologous treatments and second-generation CAR Ts.

After novel drugs receive central approval by the EMA, each European member state handles its own approval and reimbursement procedure. With list prices of approximately 289,550 EUR (373,000 USD) in the US and 320,000 EUR in Europe, CAR T-cell therapies belong to the most expensive cancer treatments at the moment. This has consequently raised concerns regarding patient access to these therapies and the financial sustainability of health care systems in general. CAR T-cell therapies are expected to bring substantial health benefits, but also exposes healthcare systems to very large expenditures. Simultaneously, an increase in trial activity heralds an expansion of CAR T-cell therapies to many more indications in the near future, of which hematological cancers currently play the most significant role.³⁵⁴ Therefore, these therapies may have a considerable incremental budget impact on healthcare expenditures, especially in the field of hematology-oncology. Moreover, the costs associated with these therapies are not limited to acquisition costs alone. Other costs that will have a substantial impact on healthcare expenditures are hospitalization, intensive care unit (ICU) stays, as well as other costs related to the treatment of adverse events and laboratory work. Furthermore, patients who live longer will also incur future medical costs unrelated to their condition for which they received CAR T-cell therapy. Conversely, longer survival may also lead to a return to productive work of survivors in remission.

In addition, substitution effects may reduce the financial impact of CAR T-cells such as avoiding the current standard of care treatment and a potential reduction in the numbers of autologous and/or allogeneic stem cell transplantation following treatment.

Overall, the application of CAR T-cell therapies may result in higher overall healthcare spending and opportunity costs –money can only be spent once– leading to a change in the allocation of the available healthcare budget. Without any formal assessment with regards to the financial aspects of these therapies, their costs remain intangible and vague. Even though economic evaluations and budget impact analyses can shed light on the economic burden

of new therapies in general, such assessments are not formally required in most countries (in Europe and elsewhere) for drug reimbursement decision making and therefore such data are scarce.

The European Hematology Association (EHA) is concerned about the sustainability of the pricing of new oncological treatments, and in particular of CAR T-cell therapy, possibly exposing health systems to very large expenditures. Therefore, the EHA has commissioned the Institute for Medical Technology Assessment (iMTA) to forecast future health expenditures, based on the adoption of CAR T-cell therapies in hematological cancers.

This study aimed to estimate the costs and budget impact associated with CAR T-cell therapies for current and future indications in hematological cancers in Europe from 2019 to 2029. The results of this study can be used by health care decision-makers in their budgetary planning as they elucidate the future economic burden of CAR T-cell therapies in several European countries.

METHODS

We followed a four-stepped approach and focused on six European member states: the former EU-5 (i.e. Germany, Spain, France, United Kingdom, and Italy) and the Netherlands. First, we conducted a review of list prices, health technology assessment (HTA) reports, budget impact analysis (BIA) dossiers, and published cost-effectiveness analyses (CEA). Second, we identified potential future indications and estimated the eligible patient population for both registered and selected upcoming indications. Third, we validated our findings with international clinical experts in the field of hematology-oncology. Finally, based on the gathered information in the previous steps, we predicted the ten-year health expenditures on CAR T-cells for several hematological cancers in the selected EU member states. The forecast entails different cost calculations namely: i) costs of CAR T-cell therapies only; ii) costs of CAR T-cell therapies and costs of care, as well as iii) incremental costs associated with the substitution of former therapies by CAR T-cell therapies.

Review of list prices and cost-effectiveness publications

We retrieved list prices for tisagenlecleucel and axicabtagene ciloleucel from HTA/BIA reports published by national reimbursement authorities. In addition, we searched for published CEA studies to complement potential missing or unpublished data. These publications were searched through EMBASE on 09-05-2019 with an update search on 20-04-2020 (see one Appendix 8A for the full search strategy). Only economic evaluations for hematological diseases were included.

Identification of future indications and estimation of the eligible patient population

To identify future indications for CAR T-cells, we searched clinictrials.gov for all registered studies on CAR T-cell therapies (search term: “chimeric antigen receptor”) for hematological cancers on 03-05-2019. This search included early phase 1, phase 1, phase 2, phase 3, and phase 4 trials. All studies were ranked according to the indication studied (most to least often studied indication). Through a semi-structured interview, several clinical experts were asked to validate this ranking and to (re)arrange it according to the sequence of expected market entry.

To estimate the eligible patient population for CAR T-cells, we focused on the two indications for which CAR T-cells already have market authorization (pALL and DLBCL) and the top five potential future indications identified by the clinical experts. The eligible patient population was calculated based on previous population forecasts by using two data sources, namely Eurostat and Globocan.⁷

In the Eurostat forecast, several assumptions were made on the future development for fertility, mortality, and net migration to predict the population of European member states to the year 2080 (based on the population in 2016).³⁵⁵ We assumed a linear trend between the 2016 and 2080 Eurostat data and calculated the yearly population per country of interest. For our purpose, we defined the *disease incident population* by estimating the yearly crude incidence rate (IR) per 100,000 for each disease and country of interest. For pALL and DLBCL, the yearly disease IRs were taken from HTA/BIA reports. For future indications, or in the absence of published data from HTA/BIA reports, we used data from the European Cancer Information System (ECIS).³⁵⁶ Subsequently, the crude IRs were applied to projected population data by Eurostat.³⁵⁵

The online database GLOBOCAN offers information on projected IRs of different cancer types for the time between 2018 and 2040 for several countries.³⁵⁷ To derive the number of patients for each cancer subtype of interest, we applied proportions based on the literature.^{358–361}

Both forecast approaches are depicted in Figure 1.

The proportion of *patients eligible for CAR T-cell therapy* per country was calculated based on HTA/BIA reports. Most publications stated the yearly number of incident cases and the total number of patients eligible for CAR T-cell therapy. From these numbers, we calculated the proportion of eligible patients and applied this rate to all incident cases to derive the total yearly number of eligible patients for CAR T-cells per disease and country. The CAR T-cell therapy eligible patient population for all future indications was based on expert opinion.

Validation with clinical experts

Clinical experts in the field of hematology-oncology were asked to validate our intermediate findings via semi-structured interviews. Respondents were asked about their experience with

CAR T-cell therapies, possible future hematological indications, resource use during pre-treatment, treatment, and post-treatment with CAR T-cell therapies in their own country, and the plausibility for CAR T-cell therapies to be manufactured within specialized hospitals (point-of-care manufacturing).

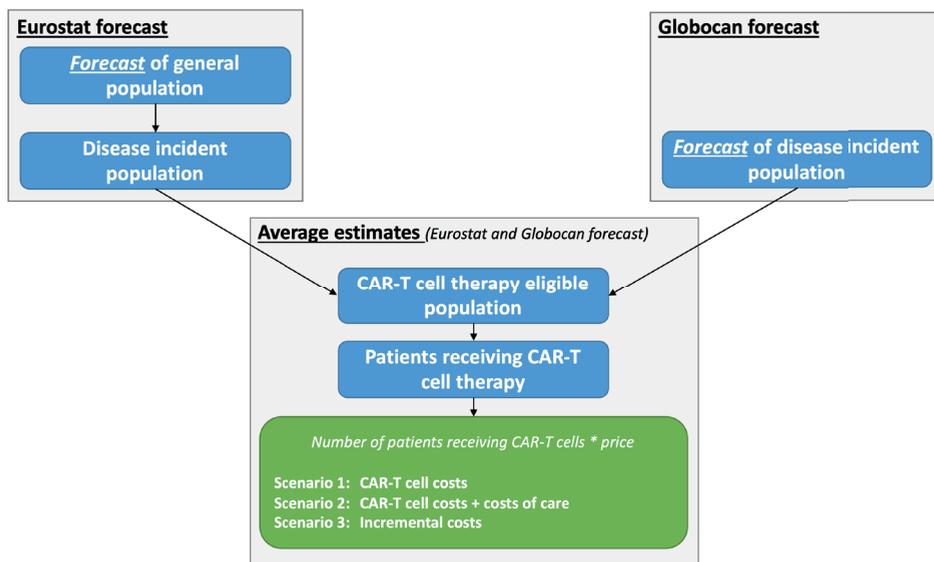


Figure 1: Flowchart of forecast approaches

Expenditure estimation of CAR T-cell therapies for current and selected future indications

Expenditures were estimated for three scenarios. In *Scenario 1*, the CAR T-cell therapy eligible patient population was multiplied with the average list price for the currently approved CAR T-cell therapies in the former EU-5 and the Netherlands. For all new indications, the costs for CAR T-cell therapies were assumed to be similar to the average list price.

For *Scenario 2*, we added costs for pre-treatment, concomitant medication, adverse events (AEs), and hospitalization (including follow-up) to the price of CAR T-cell therapy. Information on resource use (i.e. medication dosage and the number of hospital days etc.) were taken from available HTA/BIA reports or based on expert opinion. Prices for medication, hospitalization (including ICU admission), and AEs were based on costs reported in HTA/BIA reports or the literature.^{307,362–367} In case country-specific prices could not be found, the average of available prices was used. Finally, clinical experts were asked to validate these data.

For *Scenario 3*, we calculated the incremental costs of CAR T-cell therapy, i.e. the costs of *Scenario 2* minus the costs of care as usual. These incremental costs were derived from the published CEAs identified for this study. Thereafter, we multiplied the eligible patient popu-

lation with incremental costs of CAR T-cell therapy. Average incremental costs observed in DLBCL were used to estimate incremental costs for future indications.

For all scenarios and indications, we assumed a market penetration rate of 45% in the first year after registration and 90% thereafter.³⁶⁸

RESULTS

Results of list prices and cost-effectiveness publications

HTA reports and BIA dossiers were found for Germany,^{369–371} France,^{372–374} the UK^{375–377} the Netherlands^{378–380} and Spain. Only in German publications, list prices were stated for all indications. In France, all prices were marked as confidential, and in the UK, prices were stated for all indications treated with tisagenlecleucel. The UK price for axicabtagene ciloleucel was marked confidential, i.e. it was concealed in the report. Dutch prices were available for axicabtagene ciloleucel and tisagenlecleucel.

For Italy and Spain, HTA/BIA reports were not publicly available. List prices for these countries were retrieved from documents of the Italian Medicines Agency (AIFA),^{381,382} and the Spanish Ministry of Health.^{383,384} Table 1 presents an overview of all list prices.

Table 1: Overview of list prices

Country	List price (excl. VAT)		
	Axicabtagene ciloleucel (Yescarta®)	Tisagenlecleucel (Kymriah®)	
	DLBCL	pALL	DLBCL
France	350,000 EUR	320,000 EUR	320,000 EUR
Germany	327,000 EUR	320,000 EUR	320,000 EUR
Italy	327,000 EUR	300,000 EUR	300,000 EUR
The Netherlands	327,000 EUR	320,000 EUR	320,000 EUR
Spain	327,000 EUR	320,000 EUR	320,000 EUR
UK	300,000 GBP	282,000 GBP	282,000 GBP

The initial literature search detected nine cost-effectiveness analyses,^{385–388,388–392} and the search for grey literature found three HTA reports^{393–395} and one report from an ERG (Evidence Review Group) for a NICE STA.³⁸⁸ Two publications were added following the update search.^{389,396} The publication by Walton et al. (2019)²⁵ presented results from the ICER HTA report and is therefore included in the following summary, instead of the HTA report. Most studies focused on pALL patients, while three publications^{391,392,397} studied relapsed/refractory (r/r) DLBCL as indication. The ICER report³⁹³ presented results for both r/r pALL and r/r DLBCL.

The results are summarized in Table 2.

Table 2: Overview of cost-effectiveness analysis publications

Author, year	Indication, treatment	Base-case settings	Scenario analysis	Total costs	Total effects in QALYs	ICER: CAR T-cell versus
Lin et al. ³⁸⁵ , 2018	pALL, Tisagenlecleucel	Perspective: health care Horizon: lifetime Discount rate (costs/effects): 3%/3%	Yes, 5-year relapse-free survival rates (i.e. 40% - 0%)	[2017 USD] Clo-M: 314,000 Clo-C: 374,000 Blina: 282,000 CAR T-cell: 599,000	Clo-M: 3.12 Clo-C: 3.52 Blina: 3.57 CAR T-cell: 8.74	[USD/QALY] Best-case scenario (40% 5-year relapse-free survival rate): Clo-M: 61,315, Clo-C: 43,103, Blina: 50,712
Whittington et al. ³⁸⁶ , 2018	pALL, Tisagenlecleucel	Perspective: health care Horizon: lifetime Discount rate (costs/effects): 3%/3%	Yes, other discount rates, different survival curve fitting, future health care cost (included / not included)	[2017 USD] Clo-M: 337,256 CAR T-cell: 666,754	Clo-M: 2.10 CAR T-cell: 9.28	[USD/QALY] Base-case scenario: 46,000
Sarkar et al. ³⁸⁷ , 2018	pALL, Tisagenlecleucel	Perspective: health care Horizon: lifetime Discount rate (costs/effects): 3%/3%	No	[2017 USD] Clo-C: 440,600 CAR T-cell: 968,800	Clo-C: 8.58 CAR T-cell: 16.76	[USD/QALY] Payer perspective: 64,600
Walton et al. ³⁸⁸ , 2019	pALL, Tisagenlecleucel	Perspective: NA Horizon: lifetime Discount rate (costs/effects): 3.5%/3.5%	No	[2017 GBP] Salvage chemo: NA Blina: NA CAR T-cell: NA	Salvage chemo: NA Blin: NA CAR T-cell: NA	[GBP/QALY] Deterministic: Salvage chemo 45,397, Blina: 27,732
Furzer et al. ³⁸⁹ , 2020	pALL, Tisagenlecleucel	Perspective: Public insurer Horizon: 60 years Discount rate (costs/effects): 1.5%/1.5%	Yes, long-term cure rates varying between 10% and 40%	[2018 USD] Comparator (combination of chemo and HSCT): 86,597 CAR T-cell: 442,098	Comparator: 5.05 CAR T-cell: 14.90	[USD/QALY] Optimistic scenario: 53,933

Table 2: Overview of cost-effectiveness analysis publications (*continued*)

Author, year	Indication, treatment	Base-case settings	Scenario analysis	Total costs	Total effects in QALYs	ICER: CAR T-cell versus
Thielen et al., 2020 ³⁹⁶	pALL, Tisagenlecleucel	Perspective: Societal Horizon: lifetime Discount rate (costs/effects): 4%/1.5%	Yes, different perspectives, shorter plateau phase, different time horizons, alternative standardized mortality rate input, vial sharing assumed, longer duration of IWIG administration, different parametric extrapolation models resulting in different cure rates	[2018 EUR] Clo-M: 160,803 Clo-C: 193,920 BlinaL 267,259 CAR T-cell: 552,679	Clo-M: 0.74 Clo-C: 1.70 Blina: 2.25 CAR T-cell: 11.26	[EUR/QALY] Base-case Clo-M: 36,378 EUR/QALY Clo-C: 31,052 EUR/QALY Blina: 31,682 EUR/QALY
Roth et al. ³⁹¹ , 2018	DLBCL, Axicabtagene ciloleucel	Perspective: health care Horizon: lifetime Discount rate (costs/effects): 3%/3%	Yes, patients in long term remission experience 10% or 20% lower survival compared to age-matched US general population	[2018 USD] R-DHAP: 172,737 CAR T-cell: 552,921	R-DHAP: 1.13 CAR T-cell: 7.67	[USD/QALY] Base-case scenario: 58,146
Lin et al. ³⁹⁷ , 2019	DLBCL, Tisagenlecleucel and Axicabtagene ciloleucel	Perspective: health care Horizon: lifetime Discount rate (costs/effects): 3%/3%	Yes, PFS at 5 years: Axicabtagene: 40% to 20% and Tisagenlecleucel: 35% to 15%	[2018 USD] Combination: R-DHAP, R-GDP, R-GEMOX, R-ICE, SCT: 169,000 Axicabtagene ciloleucel: 651,000 Tisagenlecleucel: 529,000	Combination: R-DHAP, R-GDP, R-GEMOX, R-ICE, SCT: 1.78 Axicabtagene ciloleucel: 5.50 Tisagenlecleucel: 3.92	[USD/QALY] Axicabtagene ciloleucel versus combination (40% 5-year progression-free survival): 129,570, Tisagenlecleucel versus combination (35% 5-years progression-free survival): 168,224
Whittington et al. ³⁹² , 2019	DLBCL, Axicabtagene ciloleucel	Perspective: public payer care Horizon: lifetime Discount rate (costs/effects): 3%/3%	Yes, different extrapolation of OS and PFS curves, different perspectives, different time horizons	[Year not clear USD] R-DHAP: 151,200 CAR T-cell: 554,700	R-DHAP: 3.37 CAR T-cell: 9.19	[USD/QALY] Public payer perspective, standard parametric: 230,900

Identification of future CAR T-cell indications

The search on clinicaltrials.gov resulted in a total of 246 studies, of which most were attributed to non-Hodgkin's lymphoma (N = 97), followed by ALL (N = 84), multiple myeloma (MM) (N = 38), chronic lymphocytic leukemia (CLL) (N = 22), acute myeloid leukemia (AML) (N = 19), and others (N = 35). Several studies addressed multiple indications and targets. The three most studied target antigens were CD19 (N = 161), followed by BCMA (N = 19) and CD22 (N = 20).

The clinical experts expected that mantle cell lymphoma (MCL), follicular lymphoma (FL), MM, CLL, and AML, would be the first indications for which CAR T-cell therapy would become available in the near future. Based on phases of the clinical trials and clinical expert opinion, we estimated market entry of CAR T-cell therapies for MCL in 2021. For the indications of MM, CLL, and FL market entry was estimated for the year 2022. Finally, it was expected that CART T-cell therapies for AML would be available in 2025.

Estimation of the eligible patient population

Reported yearly IRs varied not only across but also within countries. Although targeting the same indication, HTA/BIA reports for DLBCL stated different yearly incidences for the same indication and hence different numbers of eligible patients within the same country. For our analysis, we used country averages for pALL and DLBCL in case more than one estimate was available. IRs for MCL, FL, AML, MM, and CLL were taken from ECIS (see online Appendix 8G).

The proportion of eligible patients for CAR T-cell therapies were available for pALL in Germany, France, and the Netherlands and varied between 6% (FR) and 11% (DE). For DLBCL the proportions were known for Germany, France, the UK, and the Netherlands, varying between 12% (FR) and 22% (UK). Missing data for these indications (i.e. pALL and DLBCL) in all other countries were imputed with the mean proportion from countries with available data (see for details online Appendix 8G).

To estimate the number of patients for the different cancer sub-types from Globocan, we used US figures, since European data were not available. As proportions were not available from one single source, data for pALL were based on the Surveillance, Epidemiology, and End Results Program (SEER) of the US National Cancer Institute.³⁹⁸ Most recent data for ALL and CLL were taken from the 2019 facts and figures sheet published by the American Cancer Society,³⁵⁸ and DLBCL estimates were based on Li et al.³⁹⁹ Proportions of MCL and FL patients from non-Hodgkin lymphoma were taken from Sandoval-Sus et al.³⁶⁰ (2017) and Cerhan et al.³⁵⁹, respectively.

For the period 2019-2029, we estimated a total average of 103,750 patients being eligible for CAR T-cell therapies, ranging from 95,954 patients (Eurostat forecast) to 111,545 patients (Globocan forecast) for the indications pALL, DLBCL, MCL, FL, AML, CLL, and MM.

Expenditure estimation of CAR T-cell therapies for current and selected future indications per scenario

Scenario 1 estimation based on list prices

Multiplying costs for CAR T-cell therapies with the number of eligible patients in the former EU-5 and NL resulted in average cumulative expenditures varying between 1.4 billion EUR for the Netherlands to 6.7 billion EUR for Germany. Cumulative expenditure estimates in our base-case for pALL, DLBCL, MCL, FL, AML, CLL, and MM for all included countries from 2019 to 2029 were on average 0.8 billion EUR, 13.5 billion EUR, 2.3 billion EUR, 6.4 billion EUR, 1.2 billion EUR, 0.9 billion EUR, and 3.5 billion EUR, respectively (total average: 28.5 billion EUR). Figure 2 depicts the yearly average forecasted expenditure per country for scenario 1 across all indications.

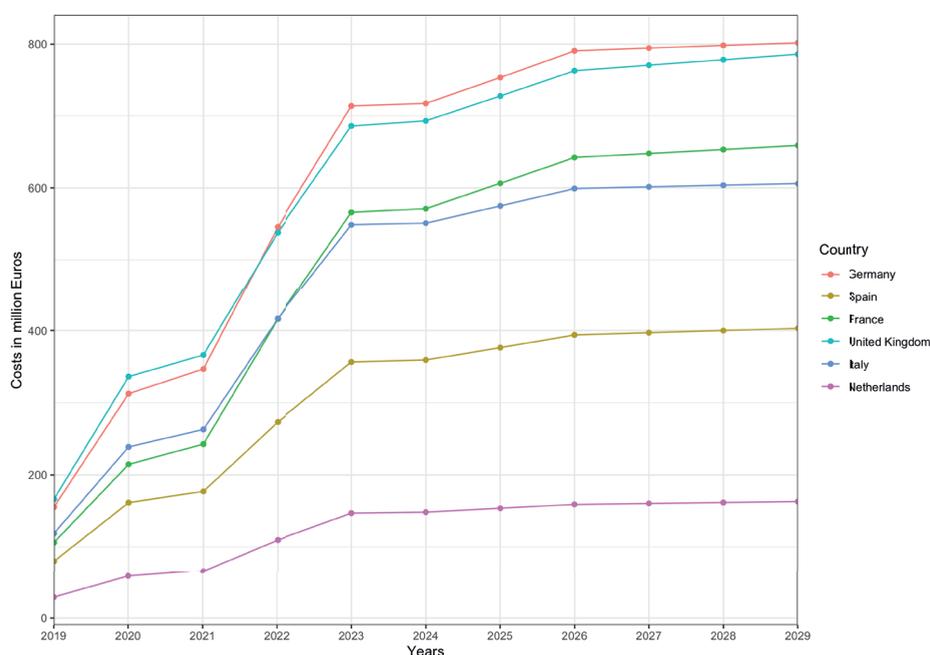


Figure 2: Total average costs per country in scenario 1 (all indications)

Scenario 2 Total CAR T-cell therapy costs, including pre- and post- costs

Resource use and prices for the cost items considered for scenario 2 could partly be retrieved from sources for the Netherlands, the UK, Germany, and France (see Table 3 for an overview of the average resource use and cost prices). The additional costs for CAR T-cell therapy amounted to 50,359 EUR for each patient receiving CAR T-cell therapy, with a substantial amount necessary for lymphodepletion and administering CAR T-cells, namely 26,615

Table 3: Cost components and resource use of pre- and post- CAR T-cell therapy

Item	Type	Value in EUR
Leukapheresis and cryopreservation	Costs	4,947
CAR T-cell administration + Lymphodepletion	Costs	15,033
ICU stay (per day)	Costs	1,444
Hospital stay at hematology/oncology ward (per day)	Costs	628
Intravenous immunoglobulin IVIG (per dose)	Costs	2,032
Tocilizumab (per event)	Costs	1,483
Treatment of febrile neutropenia (per event)	Costs	4,953
Treatment of anemia (average costs per event, incl. transfusion)	Costs	2,961
Treatment of thrombocytopenia (per event)	Costs	2,417
Oncologist/hematologist (per visit)	Costs	145
Neurologist (per visit)	Costs	103
MRI scan (per scan)	Costs	214
PET-CT scan (per scan)	Costs	1,110
Percentage of patients receiving tocilizumab	Resource use	60%*
Percentage of patients receiving IVIG	Resource use	24%
Assumed average number of days in hospital (including pre- and post-treatment)	Resource use	14
Assumed average number of ICU days (including pre- and post-treatment)	Resource use	2
Percentage of patient admitted to ICU	Resource use	20%*
Probability of patients with cytokine release syndrome (CRS) ≥ 3	Resource use	18%
Probability of patients with febrile neutropenia (FN)	Resource use	23%
Probability of patients with neurological events ≥ 3	Resource use	20%
Probability of patients with anemia	Resource use	27%
Probability of patients with thrombocytopenia	Resource use	19%
Duration of follow up (in years)	Resource use	15*

* = based on clinical experts

EUR EUR. In Table 4, these costs are shown. Cumulative expenditure estimates in our base-case for pALL, DLBCL, MCL, FL, AML, CLL, and MM for all included countries from 2019 to 2029 were on average 0.9 billion EUR, 15.7 billion EUR, 2.5 billion EUR, 7.4 billion EUR, 1.4 billion EUR, 1.1 billion EUR, and 4 billion EUR, respectively (total average: 32.8 billion EUR).

Multiplying the total costs of pre- and post- CAR T-cell care with the number of eligible patients per indication and country resulted in total cumulative expenditures between 7.7 billion EUR (DE) and 1.6 billion EUR (NL). Figure 3 depicts average forecasted costs (all indications) per country for scenario 2.

Table 4: Average total costs pre- and post- CAR T-cell administration in former EU-5 and NL

Item	Value in EUR
Average cost of care pre- CAR T-cell administration	7,147
Average cost lymphodepletion and administering CAR-T	26,615
Average cost of care managing AE's	10,524
Average cost of follow up	6,074
Total cost of pre and post- CAR-T care	50,359

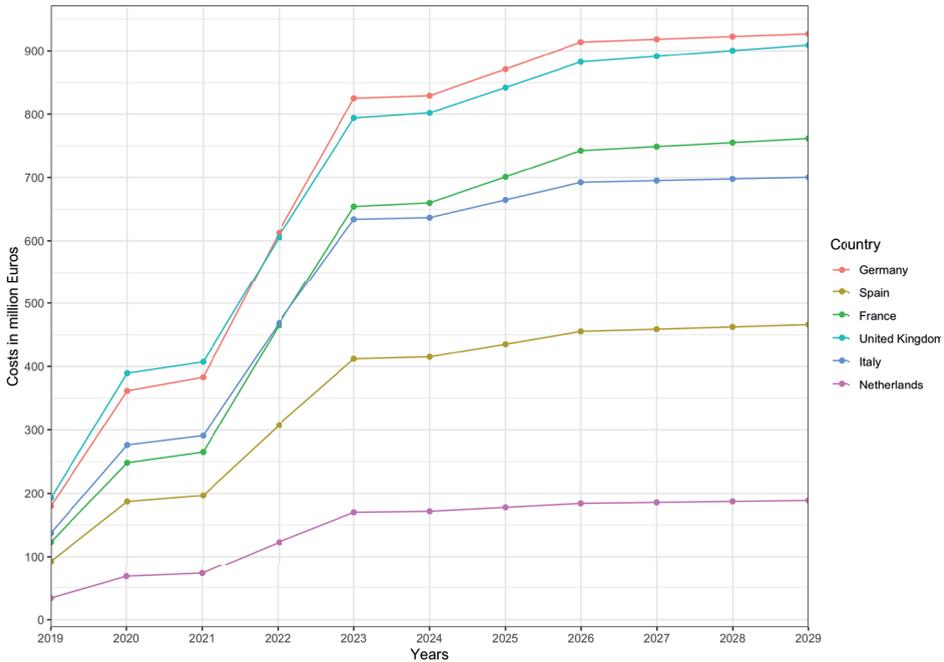


Figure 3: Total average costs per country in scenario 2 (all indications)

Scenario 3 Incremental costs of introducing CAR T-cell therapy

Of all CEA studies reviewed, the total average incremental costs of CAR T-cell therapies when compared to care as usual were 276,086 EUR and 328,727 EUR for patients with pALL and DLBCL, respectively. Cumulative expenditure estimates in our base-case for pALL, DLBCL, MCL, FL, AML, CLL, and MM for all included countries from 2019 to 2029 were on average 0.7 billion EUR, 13.8 billion EUR, 2.3 billion EUR, 6.5 billion EUR, 1.2 billion EUR, 0.9 billion EUR, and 3.5 billion EUR, respectively (total average: 28.9 billion EUR).

Figure 4 depicts the average expenditure across all countries and indications of all three scenarios. The upper and lower bounds are the estimates based on the Globocan and Eurostat approach, respectively.

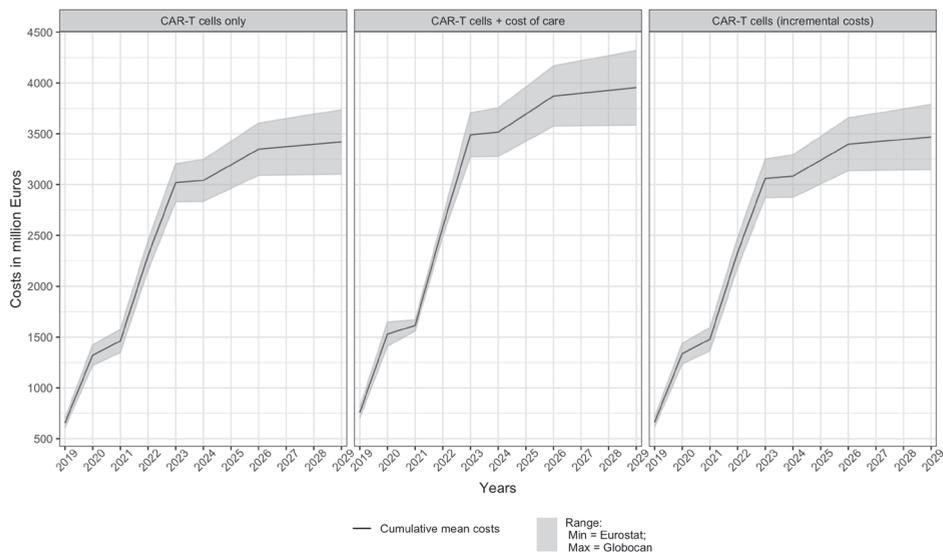


Figure 4: Expenditure forecast per scenario (all countries and indications)

DISCUSSION

In our analysis, we estimated future expenditures associated with CAR T-cell therapies for a set of hematological indications in six European member states between 2019 and 2029. The average cumulative costs in all six countries for all included indications were estimated at 28.5 billion EUR (scenario 1) with a steady increase in yearly average costs across the time range studied. Average yearly costs increased in a step-wise manner which can be explained by the assumed drug penetration rate and predicted new indication launches. For the year 2019, we assumed penetration rates of 45% for current CAR T-cell therapies for DLBCL and pALL. This penetration rate peaks in 2020 (90%) and remains stable thereafter. For the year 2021 we assumed new product launches for MCL and in the year 2022 new launches for FL, MM, and CLL. Even with an initial penetration rate of 45% for the first year of the product launch, this is a major cost driver that more than doubled the yearly average costs. Finally, the product launch for AML was estimated for the year 2025 and is responsible for another stepwise increase in predicted yearly cumulative costs.

It seems obvious that new product launches have a considerable impact on any expenditure. Therefore, the methodology for estimating the expenditure of these launches is crucial. However, there is no reliable way of knowing at what time exactly new CAR T-cell therapies will be available for treatment. For product launches of future indications, we used data on available clinical trials on clinicaltrials.gov and estimated their future availability based on the time between the trial start date and the published date of the respective HTA reports for tisagenlecleucel and axicabtagene ciloleucel. In case several trials were currently running,

we selected studies from the biggest sponsor in terms of market capitalization. However, this approach neglects the possibility of failing trials that would not lead to market access of a drug, the possibility of smaller companies to be the first to receive market access for their drug, or the possibility of postponing market access due to internal decisions. Therefore, we validated our findings with clinical experts who suggested CAR T-cell therapy launches in the years 2021 and 2022 for MCL and FL, respectively.

The eligible patient population for CAR T-cell therapies in the different EU member states was based on the population projection by Eurostat³⁵⁵ with fixed incidence rates, and the incidence projection from Globocan, over the period 2019 to 2029. Both strategies were used to congregate an average patient population. The factual eligible patient population could deviate from our projection due to unforeseen events and assumptions. Our assumptions and results were validated by clinical experts, but forecasts are sensitive to changes in outcomes and business strategies. Besides, future clinical pathways may also change, accommodating for new treatments that are currently in the pipeline. Advancements in other immunotherapies and targeted therapies could affect future uptake of CAR T-cell therapies as well. Currently, available CAR T-cell therapies (i.e. tisagenlecleucel and axicabtagene ciloleucel) are being investigated for the second-line treatment of patients with DLBCL (NCT03570892, NCT03391466) which will make those therapies available to an even larger patient population. Moreover, lisocabtagene maraleucel is also being investigated in a second-line setting for patients with B-cell non-Hodgkin lymphomas (NCT03575351). If CAR T-cell therapies are utilized in second-line settings, this would considerably increase the eligible patient population.

Besides the uncertainties regarding the number of patients eligible for CAR T-cell therapies, the price of the therapy itself is associated with a high degree of uncertainty. For our analysis, we used list prices whenever available. However, actual prices for CAR T-cell therapies are mostly subject to confidential negotiations. Hence, the actual price per country is unknown. For our analysis, the price of CAR T-cell therapies for future indications was assumed to be 323,500 EUR per treatment, based on an average of the known list prices for DLBCL patients. This estimation could be inaccurate, due to existing and future competing treatment options. Moreover, clinical experts already reported a new and lower price for tisagenlecleucel in Germany of 275,000 EUR per treatment. Such a price reduction could be the result of the two CAR T-cell therapies (i.e. tisagenlecleucel and axicabtagene ciloleucel) currently competing for DLBCL. The expected approval of lisocabtagene maraleucel⁴⁰⁰ (Celgene) could drive up competition even more. To allow competition with the two existing CAR T-cell therapies, could lead to an even further reduction in prices. Per contra, Celgene might price lisocabtagene maraleucel higher than its competitor considering the possibility of being best-in-class.⁴⁰¹ Yet another scenario that could affect prices of CAR T-cell therapies is the point-of-care production within hospitals, leaving health care payers with only the manufacturing costs. Specialized hospitals in several countries are exploring the possibility

to make their own CAR T-cell treatments in the future. We have asked clinical experts whether they think it would be an option for lowering the price and improving the access to CAR T-cells for patients. In Germany and the Netherlands, the probability was estimated above 50% and the cost of own production was estimated to be 50,000 EUR – 70,000 EUR per CAR T-cell treatment. This means that one treatment may cost approximately 80,000 EUR (including pre- and post-care costs) instead of 375,000 EUR. In the literature, the manufacturing costs have been estimated at 65,000 USD.⁴⁰² Moreover, companies such as Cellectis or Servier are currently working on the development of allogeneic CAR T-cell therapies (NCT03190278, NCT02808442). These off-the-shelf CAR T-cell therapies could be manufactured in batches instead of on-demand, resulting in economies of scale, and possibly lower cost for health care payers. Lastly, the possibility of *in vivo* reprogramming of T cells, to e.g. be active against CD19 positive cells, could potentially reduce treatment costs by circumventing *ex vivo* manufacturing of T cells.⁴⁰³

While the price for CAR T-cell therapies may be subject to changes, the cost of care associated with CAR T-cell therapy could also decrease over time. This may be due to possible reductions in side-effects or different adverse event profiles with future CAR T-cell therapies. Likewise, our forecasted incremental costs may differ. Our estimates are based on relatively scarce cost-effectiveness data on both tisagenlecleucel and axicabtagene ciloleucel. For future indications, we assumed an average of the known costs. However, according to clinical experts, the incremental costs associated with CAR T-cell therapies for MM could be much lower when compared to DLBCL for instance. This may be caused by the chronic nature of MM and its current high costs for the standard of care, which could be redundant after CAR T-cell therapies.

Other cell and gene therapies that have regenerative or curative potential are currently being developed for various indications.⁴⁰⁴ The limited duration of clinical trials, is coincidentally accompanied by uncertainty in long-term effects. Moreover, the possibility to cure patients with a single administration presents a new challenge for pricing and reimbursement of these therapies.⁴⁰⁵ Current pricing of gene therapies ought to reflect expected long-term effects and its curative potential. For instance, Novartis has priced Zolgensma, a gene therapy medication used to treat spinal muscular atrophy in children less than 2 years old, at approximately 1.887 million EUR (2.125 million USD), which makes it the most expensive drug currently available.⁴⁰⁶ Spark Therapeutics Inc's Luxturna gene therapy for patients with inherited retinal disease, was priced at approximately 754,817 EUR (850,000 USD) for both eyes. One aspect these cell and gene therapies share is their high prices which are often justified by significant treatment effects. However, long-term efficacy results are not yet available, and some patients may need subsequent CAR T-cell therapies or allogeneic stem cell transplantation. In addition, some patients might need additional (other) gene therapies in the future. It remains unclear who should bear the financial risk stemming from the uncertainty in the clinical value. Consequently, reimbursement decision-makers in many

EU member states seem to be reluctant in applying “standard” reimbursement criteria to CAR T-cell therapies.

Several EU member states and the UK adopted various pricing and reimbursement schemes. While France and the UK opted for coverage with evidence development schemes, both Italy and Spain negotiated outcomes-based staged payment agreements. Outcomes-based rebates were negotiated in Germany, and in Austria, different cost-sharing agreements are in place, varying between provinces. In the Netherlands tisagenlecleucel for pALL, patients is reimbursed through standard criteria, since its estimated budget impact was found to be relatively low (approximately 10 children per year were estimated to be eligible). Axicabtagene ciloleucel for DLBCL patients on the other hand was placed in the so-called ‘lock’ for 421 days, before being reimbursed. The different reimbursement schemes for the former EU-5 are analyzed and discussed in depth elsewhere.⁴⁰⁷

At the 2020 EHA/EBMT CAR T-cell congress in Sitges, manufacturers signaled a willingness to further cooperate with payers reaching reimbursement agreements. Presented options were discounts of list prices, price-volume agreements, outcome-based agreements based on patient-level outcomes, value-based agreements based on additional clinical evidence, or a price by indication. Despite this, CAR T-cell therapies are still not affordable for many countries.

We limited our study to the former EU-5 and the Netherlands, all of which are already reimbursing CAR T-cell therapies. However, difficulties regarding reimbursement are even greater in Eastern Europe, resulting in many patients currently lacking access to these promising treatments.

future market of CAR T-cell therapies has been studied previously, although not with a specific focus on hematology-oncology. The decision resources group (DRG) for instance published a report on CAR T-cell therapies in the pipeline and a forecast snapshot. Without revealing the employed methodology, the DRG estimated the CAR T-cell therapy market at approximately 1.5 billion EUR (1.7 billion USD) by 2026 for the hematological malignancies. It is not clear whether these figures ought to reflect the US, European, or a global market. Our estimation exceeds the DRG figures by far but since the methodological approaches cannot be compared, it remains open which forecasted aspects differ.

Another study estimated 114,737 cumulative treated patients in the US between the years 2019 and 2029 for all hematological cancers.³⁶⁸ This is relatively close to our estimate considering a fundamentally different methodological approach and the inclusion of different cancer types. In terms of costs, Quinn et al.⁴⁰⁸ mention a range between 11.1 billion EUR (12.5 billion USD) and 88.8 billion EUR (100 billion USD) for all hematological cancers. Our estimates fall within this range. However, it needs to be noted that although the US population is comparable to the studied population in terms of size (US population is roughly 96% of the former EU-5 + NL), costs for CAR T-cell therapies are generally higher in the US.

Finally, we conclude that, although current and future CAR T-cell therapies seem promising in hematological cancers, with the current price-setting the financial burden on health care systems in former EU-5 and the Netherlands is considerable. Some European countries are struggling with associated costs of pre- and post- care for CAR T-cell therapies as these costs are reimbursed insufficiently. Further, the pricing of CAR T-cell therapies is high and it can be expected that new and commercial CAR T-cell therapies will be in a similar price range. Combined with the expected expansion of indications, the financial burden on health care systems will increase substantially with direct effects on patient access to these new treatment options. Specialized hospitals could produce CAR T-cell treatments themselves in the future at lower costs, which could drive procurement costs down. Stimulating this development may contribute to better patient access but future research and development from manufacturers must be guaranteed.

Chapter 9

General discussion

Cancer is the second leading cause of death after cardiovascular diseases in Europe, accounting for 26% of all death in 2016.² During the last three decades, the worldwide incidence of cancer increased by 50%, while mortality due to cancer increased with 20% during the same time frame.²

Novel treatment options such as chimeric antigen receptor (CAR) T cells are on the verge of revolutionising the field of haemato-oncology as they have the potential of actually curing certain types of cancer.⁴⁰⁹ Nevertheless, prices for novel cancer drugs in general and for haematologic malignancies in particular, are high and increasing throughout the last decades.⁴⁵ To keep healthcare systems affordable, decision makers have adopted several measures to control the price at which novel treatments are reimbursed. Through a formal Health Technology Assessment (HTA), the value that patients and health systems perceive for the particular treatment can be assessed, and a price for reimbursement can be set accordingly.⁷ Although the concept of HTA is already used since the 1980's, various challenges persist to this day.

Recently, the *European Network for Health Technology Assessment* (EUnetHTA) defined nine domains of HTA. This dissertation mainly focussed on identifying and addressing challenges in the domain of *costs and economic evaluation*. In addition, the domains of *safety*, *clinical effectiveness*, as well as *patient and social aspects* were taken into account. More specifically, this dissertation explored several challenges in assessing costs and cost-effectiveness of treatments in haemato-oncology. Several aims were defined in **Chapter 1** which were analysed in three parts. PART I explored challenges in the evidence synthesis for HTA. PART II aimed at providing evidence on the cost-utility of novel and expensive treatments in haemato-oncology. PART III described implications of these cost-utility analyses (CUAs) on healthcare decision making and investigated the impact of expensive immunotherapies for the treatment of cancer on the (future) healthcare expenditure in Europe.

This final chapter discusses various aspects and findings of this dissertation and ends with recommendations for future research and healthcare policy.

PART I: CHALLENGES IN THE EVIDENCE SYNTHESIS FOR HTA

Three distinct challenges in synthesising evidence for HTA were identified and addressed in this dissertation.

Synthesising evidence from existing economic evaluations

In the context of evidence-based medicine (EBM), health decision making should be based on so-called “evidence to decision frameworks”, meaning that all relevant factors for a decision are assessed and considered both systematically and transparently.⁴¹⁰ To answer research

questions in the *costs and cost-effectiveness* domain of HTA, previously published economic evidence should therefore be reviewed systematically.¹⁷

To this end, researchers and decision makers could make use of specialised databases that focus on indexing published economic evaluations such as the U.K. *National Health Service Economic Evaluation Database* (NHS EED) or the *Health Economic Evaluation Database* (HEED). However, since funding had ended, the HEED is no longer accessible for searches since the end of 2014, and the NHS EED is no longer updated since March 2015.^{71,72} Hence, finding all relevant economic information on a specific health topic has become a challenging and (more) time consuming task. Today, researchers and policy makers need to search economic evidence through databases that primarily index biomedical literature. Ideally, the resumption of the former specialised databases on economic evaluations could solve this issue. However, the reasons that led to their cessation might probably still persist and therefore these solutions seem unlikely. Simultaneously, no authoritative guidance on how to conduct systematic reviews of economic evaluations in biomedical databases was available.

To fill this gap, **Chapter 2** aimed at supporting researchers to prepare systematic literature reviews of economic evaluations for informing evidence-based healthcare decisions. As such, **Chapter 2** details the second step of a five-stepped approach of this process. The full five steps include (1) initiating a systematic review of economic evaluations, (2) identifying full economic evaluations (see Chapter 2), (3) data extraction, risk of bias and transferability (see Wijnen et al., 2016⁷⁰), (4) reporting of results, and (5) discussion and interpretation of results. The entire approach including a brief summary of all steps is described elsewhere.³⁰

Generally, this guidance was well received in the scientific community which is reflected in several citations of this work. More specifically, the WHO-INTEGRATE (INTEGRATE Evidence) framework version 1.0, advised to gather evidence related to the review of economic analyses following the guidance provided in **Chapter 2**.⁴¹⁰ This can be viewed as some sort of validation of the guidance.

Nevertheless, the guidance may become (partly) futile or outdated in the future. This may be due to several reasons. For instance, the way databases can be searched is constantly refined. In 2016, the biomedical research database *Embase* integrated a new search form enabling the database searcher to enter search terms separately for the different aspects of the PICO (Patient, Intervention, Comparator, Outcome) scheme.⁴¹¹ The user interface then automatically suggests synonyms and combines those into a full search query.⁴¹² This feature facilitates an instant conceptualisation of the PICO scheme for the respective research question. While this might save time for the user, important synonyms could still be missed, and truncated search terms are not added. Our guidance offers suggestions to incorporate a variety of search terms and is therefore still relevant. Also, other databases do not yet provide such elaborate user interfaces. Searching *Embase* with the integrated PICO search tool might thus be a good starting point in designing a new search strategy. Subsequently, the query could be critically assessed with the guidance presented in **Chapter 2**. However, such a

process is not covered by the current version of the guidance and an update in this regard is warranted. For all other databases this guidance still offers useful resources for building a search query with a desired level of specificity and sensitivity.

The evolution of biomedical research databases may call for another update of the guidance soon. Not only because user interfaces are increasingly refined and tailored to the researchers' needs. Novel, intelligent and automated search algorithms are at the verge of changing the way literature is searched in general. Machine learning algorithms and tools are promising approaches to reduce the workload of systematic literature reviews and can be applied to inform evidence synthesis already today.^{413,414} However, such tools are still under development and may require an extensive background in information technology or biomedical informatics.^{414,415} Until such approaches have become fully mature and available to a broader audience, **Chapter 2** may serve as a practical guidance to undertake “hand-crafted” systematic searches for economic evaluations.

Synthesising evidence on effects

Data from randomised controlled trials (RCTs) are often referred to as the “golden standard” of collecting clinical evidence on safety and efficacy of a drug.³⁶ Consequently, evidence on effects for HTA is preferably collected through such studies.^{17,19,416} However, these studies are not *per se* designed to inform economic evaluations. RCTs are for instance primarily powered to detect differences in clinical outcomes. Since variables related to costs have higher variance, the required sample size to detect differences in costs is considerably higher when compared to the needed sample size to detect differences in clinical effects.^{417,418} Furthermore, clinical studies have limited follow-up times. Consequently, desired clinical benefits such as overall survival (OS) can often not fully be captured. Therefore, so-called surrogate endpoints are often chosen as primary trial endpoints. In the field of haemato-oncology, these often include event-free survival, freedom of treatment failure, or progression-free survival (PFS). Surrogate endpoints such as PFS do not usually reflect better health-related quality of life (HRQoL) or overall longevity.⁴⁵ Outcomes of the study in **Chapter 6** seem to confirm the former, since HRQoL for patients in progression-free disease did not differ from patients in progressive disease. This aspect is discussed in more detail in **Part II** of this Chapter.

Patient selection in accordance with the decision problem

The decision to reimburse a novel treatment is usually taken for a (sub-)group of patients with a specific disease. Therefore, it is important that economic evaluations clearly define the target patient population including all relevant subgroups. When data from RCTs are used to inform efficacy parameters of economic evaluation, challenges may arise. This is because RCTs are conducted under strictly controlled and idealised conditions. The selection of a narrowly defined patient population can hence potentially affect external validity, which is need when (reimbursement) decisions need to be made on a more general level.⁴¹⁹ A recent

literature review showed that the majority (71.2%) of included RCTs in cardiology, mental health, and oncology reported that their samples were not broadly representative of real-world patients.⁴²⁰ More specifically, patients enrolled in oncological studies were found to be often younger, less likely to be female, have better performance status, and better disease prognosis than real-world cancer patients.⁴²⁰

This issue poses a general challenge to the generalisability of all economic evaluations making use of RCT data, especially when the (reimbursement) decision problem focusses on specific patient subgroups of the gathered evidence.

In **Chapter 7** for instance, evidence on effects were used for a subgroup of the trial population in the final analysis. In this way the decision uncertainty for the reimbursement authority could be reduced to an extent that the treatment could be accepted for reimbursement. However, initially, the trial was not designed to detect differences in efficacy between the novel treatment and its comparator for the relevant subgroup. Consequently, *post hoc* subgroup analyses were necessary for the economic evaluation.

While *post hoc* subgroup analyses are possible for clinical trial data, the *Consolidated Standards of Reporting Trials* (CONSORT) initiative strongly criticised such approaches.⁴²¹ To allow for more robust estimates, subgroups analyses should be pre-specified and it is suggested that such specifications could be made mandatory, at least for publications.⁴²²

In **Chapter 6**, the relevant subgroup for the reimbursement decision problem were pre-stratified. Therefore, using evidence from this subgroup for the CUA did not introduce additional uncertainty. This was however only possible since patient-level data were available. Usually, such subgroups analyses cannot be performed since the relevant empirical survival data is often not published.³¹⁸

To tackle the issue of low external validity of RCT data, adapting trial designs to include more representative patient samples or supplementing RCT data with evidence from supportive studies could be a solution.⁴²⁰ Regarding evidence of specific subgroups, clearly defined and pre-specified subgroups could offer more valid and reliable outcomes, relevant for economic evaluations. In addition, such evidence should be published so that relevant cost-effectiveness studies can be conducted without having access to patient-level data.

Estimating long-term efficacy

Since clinical studies usually have restricted follow-up times and most jurisdictions prefer a lifetime horizon for economic evaluations,^{19,26} there is a need to extrapolate the empirical data to a longer time horizon. Researchers can choose between several techniques, and parametric survival models are often used for this purpose. The literature refers to the exponential, Weibull, Gompertz, log-normal, and log-logistic models as “standard” parametric models.³⁰⁶ These models are frequently used in economic evaluations and their employed methodology including their strength and weaknesses is well documented.^{211,306,423} When parametric models are used to extrapolate patient data of clinical studies, both internal and external

validity need to be verified. Internal validity is commonly assessed through visual inspection of the fitted curves to the observed survival. In addition, model fit criteria such as the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) are used for this purpose. External validity is subsequently assessed by comparing the extrapolated survival to data from other studies (when available) or the general population mortality (extrapolated data should not exceed this mortality). In addition, the plausibility of the extrapolated long-term survival should be validated by clinical experts.²¹¹

Chapters 5 and 6 employed such standard parametric survival models to extrapolate the empirical survival data of the respective clinical studies. The results showed that the internal validity of the extrapolated curves was high since all parametric survival curves visually fit the empirical data well and both AIC and BIC values did not differ to a great extent. While internal validity could be established, long-term estimates differed considerably. This aspect of survival extrapolation is long recognised in the literature.³⁰⁶ To ensure external validity in **Chapters 5 and 6**, clinical experts were consulted to validate the long-term estimates. However, as of yet, standard methods for the elicitations of expert opinion for HTA are scarce,⁴²⁴ and although some tools exist to aid in this endeavour, none of them focus on the external validation of parametric survival models.^{425–427} This may introduce some uncertainty in the elicitation process. For the studies presented in **Chapters 5 and 6**, clinical experts were asked to validate long-term survival by means of a semi-structured questionnaire in combination with subsequent telephone interviews. This may be a possible solution in the absence of a clear methodological guidance. However, depending on the complexity of the disease, renowned clinical experts may be difficult to find. For **Chapter 5** for instance, only one clinical expert could be included. This was because paediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia (pALL) are only treated in one specialised centre in the Netherlands. Consequently, the number of clinical experts available to consult about this particular indication is limited. Although for **Chapter 6** more clinical experts could be included, expert opinion in general may be biased with regard to the experts' experience, training, mood or motivation.^{428,429}

Due to these limitations, there is an expressed need to improve parametric survival extrapolations to incorporate external (long-term) data.^{430–433} Recently, Vickers (2019) evaluated several survival curve extrapolation techniques using long-term observational cancer data.⁴³⁴ The author generally concluded that long-term survival predictions can be improved by directly using such mature long-term data and recommends different methodological approaches to extrapolate survival data and to integrate long-term data, depending on the observed treatment benefit. Nevertheless, several limitations were stated with regard to the data used in the study. Most importantly, the different techniques were assessed using data from patients ≥ 80 years old, which might have led to biased results.⁴³⁴ This is particularly important to acknowledge when the suggested methodology is used to extrapolate data of patients with haematological malignancies, since in Europe, their average age at initial diag-

nosis is considerably lower (i.e. approximately 64 years; median: 69 years; standard deviation [SD] or range not reported).⁴³⁵

Extrapolating empirical survival of cancer patients remains a challenging task. And although guidance exist to support researchers in employing “standard” parametric models,²¹¹ the plethora of alternative modelling approaches such as for instance model-averaging techniques,^{436,437} hybrid models,^{438,439} or cure models⁴⁴⁰ show that this is an evolving field of research. Therefore, it seems that a definitive guidance cannot yet be issued. Future research should focus on validating promising modelling techniques to enable robust long-term estimates of survival data for the use in economic evaluations. Simultaneously, existing guidance for such methodologies should frequently be updated to incorporate newest findings and recommendations.

Choosing an appropriate treatment comparator

Since economic evaluations are comparative studies, any novel treatment that will be assessed for its cost-utility needs to be compared to at least one other course of action.

The importance of choosing an appropriate comparator for any economic evaluation is highlighted by the Drummond checklist for assessing economic evaluations.¹⁹ The second question of this checklist focusses on whether a comprehensive description of the competing alternatives was given and whether *relevant* alternatives were omitted. Already in 1998, Mullins and Ogilvie, concluded that most pharmacoeconomic guidelines agreed on an appropriate comparator being either a therapy currently used in standard practice, or a therapy that is most likely to be replaced by the novel treatment.⁴⁴¹ More recently, reviews of country-specific economic evaluation guidelines came to similar conclusions.^{442,443} Consequently, the EUnetHTA stated in its 2015 guideline that comparators should “reflect most relevant alternative intervention(s) used in clinical practice”.⁴⁴³

Despite such clear and longstanding preferences for comparators in economic evaluations, choosing a relevant comparator was challenging for **Chapters 5 and 6**. Although several treatment alternatives existed for the patient population studied in **Chapter 5**, no standard of care was yet defined. Therefore, all commonly administered treatment alternatives in the reference country, for which survival data were available, were selected for the evaluation. Similarly, no clear standard of care was defined for patients studied in **Chapter 6**. And although clinical experts indicated several treatment options for the reference country, reliable survival data of these treatments were not available.

Using phase II clinical data

Conducting pivotal phase III trials is a time-consuming effort and it can take decades until such studies are concluded. To improve a timely access for patients to new medicines, the *European Medicine Agency* (EMA) established the so-called PRIME scheme to “enhance support for the development of medicines that target an unmet medical need”.⁴⁴⁴ Consequently,

evidence from phase II clinical trials is increasingly used by the EMA to decide on the marketing approval of new (cancer) treatments.⁴⁴⁵ The question arises to what extent phase II clinical data can be used to inform early HTAs.

Following the *ISPOR Good Research Practices in Modelling Task Force*, conceptualising (decision) models for economic evaluations is an iterative process, involving several steps and stakeholders.²¹⁰ To keep the time between marketing approval and the possible reimbursement of novel and expensive treatments as short as possible, a timely beginning of conceptualising the model is warranted. **Chapter 4** demonstrated that evidence from previously published phase II studies can be used to conceptualise such a model and to simulate long-term survival outcomes. Such simulations make a *de novo* decision model transparent and discussable within the scientific community. In addition, the simulation results already indicate the magnitude of the efficacy that can be expected from the novel treatment. The proposed model in **Chapter 4**, together with its results was generally accepted by scientific peers, supporting its credibility.^{446,447} Complemented with clinical evidence from a comparator treatment and input parameters on costs, this model could be used for a model-based CUA. In such a case, an early HTA could be conceivable, accelerating later reimbursement procedures. In case results of such an analysis show that the novel treatment would result in a significantly unfavourable cost-effective ratio when compared to the pertinent willingness-to-pay (WTP) threshold, the use or development of the novel treatment could be halted. Nevertheless, the analysis of **Chapter 4** needs to be interpreted as an *indication* for the long-term survival of the studied patient population which needs to be validated through phase III clinical data. Currently, the multi-centre, international phase III clinical trial RETHRIM aims at creating such needed evidence. However, issues with patient accrual have delayed the end of the study extensively. This is due to several reasons such as improved preventive measures to develop the disease (acute graft-versus-host-disease [aGvHD] in this case) and the relatively small indication (aGvHD can be considered as rare⁴⁴⁸).

In **Chapter 5**, phase II clinical data was used to perform a formal CUA for a Dutch reimbursement dossier. Previously, the studied therapy (tisagenlecleucel) had received marketing approval following the EMA's PRIME scheme based on phase II clinical data.^{50,449} Consequently, evidence from an RCT were not available at the time the economic evaluation was conducted. With the evidence available, CUAs could be conducted in several jurisdictions, including the one of **Chapter 5**.^{254,256–258,389,450,451} Nevertheless, most European Member States did not opt for a “classic” reimbursement of the therapy. All (former) EU-5 Member States (i.e. France, Germany, Italy, Spain, and the UK) have adopted some kind of outcomes-based reimbursement scheme (OBR).⁴⁰⁷ Reasons for this included the high costs of the treatment but also the considerable amount of decision uncertainty stemming from restricted efficacy data.⁴⁰⁷ In the Netherlands, the decision to reimburse the treatment was based on a simple budget impact analysis (BIA) instead of making use of the available results of the CUA in **Chapter 5** (more about this in Part II of this discussion). Consequently, the

novel treatment was reimbursed following a standard procedure in the Netherlands and no OBR was negotiated.

Similar to the findings of **Chapter 4**, the results of **Chapter 5** need to be validated with long(er)-term efficacy data, preferably from phase III clinical data.

Synthesising evidence on costs

When economic evidence is not available or transferrable to the setting of interest, new evidence needs to be generated. **Chapter 3** can be seen as a case study to estimate healthcare costs based on two distinct approaches.

First, healthcare costs of paediatric patients with sickle cell disease were based on the pertinent clinical practice guideline (CPG). These costs could quickly be estimated since the expected resource use frequency was described in sufficient detail and could be valued with reference prices. However, such an approach only considers the *standard* resource use of patients. Consequently, it does not provide insights into real-world resource use. As such, it neglects any additional or emergency visits to the hospital for instance. Depending on the studied disease, such visits can be relatively frequent (e.g. in the case of sickle cell disease⁴⁵²) and should therefore be considered when costs are estimated.

Therefore, a second approach was explored. For this, available patient level data of a hospital financial claims database was used to gather information of real-world resource use. This approach was significantly more challenging when compared to the first one due to several reasons. For instance, receiving access to the financial claims database was complicated. Since hospital claims data are generated for billing purposes,⁴⁵³ they are usually managed by the financial department of a healthcare institution whose primary aim is not the support of scientific research. Also, claims data hold less information on patients than for instance medical records. While this makes them easily de-identifiable,⁴⁵³ it is not always clear which of the recorded measures are most useful to represent utilisation.⁴⁵⁴ This can only be resolved in a dialogue with the healthcare professionals and the data administrator.

In conclusion, hospital claims databases are not designed to support research endeavours on costs. In addition, such databases are subject to frequent updates and changes. The respective Dutch reimbursement system for instance was introduced in 2005 and profoundly revised in 2012.⁴⁵⁵ It can therefore still be considered as a system under development. Especially at the time data for the initial analysis of **Chapter 3** was requested (2017). Enhancements and updates of hospital information systems under development are necessary and important. However, such changes may render previous or newly collected data incompatible and hence not useful for data analyses. Nevertheless, claim-based studies are conducted at least since the 1980's for manifold purposes in the US.⁴⁵⁶ A review of such studies between 2000 and 2005 in five healthcare journals found that the majority used claims data to study aspects of access to healthcare (49%), followed by quality of healthcare (24%), and interventions,

therapies, or treatments (13%).⁴⁵⁷ Studies on healthcare costs were not mentioned, although some studies exist.^{458,459}

Generally, the literature suggests that using claims data to estimate the cost of illnesses is feasible and may provide access to a relatively large sample size while avoiding selection bias.^{458–461} This is in line with the findings reported in **Chapter 3**. In addition, **Chapter 3** demonstrated that hospital financial claims data can be used for the estimation of real-world healthcare costs. Supplemented with patient characteristics such as age, sex, and diagnosis, such databases can be a powerful and reliable source of information that is readily available and frequently updated. Alternatively, as mentioned in **Chapter 1**, information on resource use could be synthesised from patient questionnaires, although this may be related to some bias.⁴³ Future research could compare either approach (i.e. collecting resource use data from financial claims databases versus patient questionnaires) to establish the comparative evidence on the validity of either method.

PART II: COST-UTILITY OF NOVEL TREATMENTS IN HAEMATO-ONCOLOGY

Costs of novel cancer treatments for haematological conditions are high and can put the affordability of other new treatments at risk. Therefore, reimbursement decisions need to be made in a transparent and systematic way. CUAs can provide the needed information to make evidence-based decisions in healthcare and are therefore a vital part of the reimbursement decision process. This dissertation assessed the cost-utility of two novel and expensive treatments that entered the European market in 2019.

The cost-utility of tisagenlecleucel when compared to clofarabine monotherapy (Clo-M), clofarabine combination therapy (Clo-C), and blinatumomab (Blina) in paediatric patients with relapsed/refractory acute lymphoblastic leukaemia (pALL) was assessed in **Chapter 5**. Based on the disease burden and applicable willingness-to-pay (WTP) threshold, tisagenlecleucel could be considered cost-effective from all perspectives studied. Several other CUA assessed the same therapy in Canada,³⁸⁹ the US,^{254,257,451} and the UK.²⁵⁸ All of these studies came to the same conclusion of tisagenlecleucel being cost-effective in the base-case analysis.

Similarly, **Chapter 6** assessed the cost-effectiveness of lenalidomide plus rituximab versus rituximab monotherapy for previously treated follicular lymphoma (FL). Based on the selected WTP-threshold for the base-case analysis, lenalidomide could be considered cost-effective. However, the probabilistic sensitivity analyses indicated some uncertainty in the results. In addition, some scenarios exceeded the chosen WTP-threshold for the base-case analyses, rendering the treatment not cost-effective. To this date, two other studies are available that assessed lenalidomide in previously treated FL in the UK and China.^{316,318} While the treatment was considered cost-effective in a UK setting, the Chinese study concluded

that lenalidomide was not cost-effective. Several reasons could have led to the conclusion of the latter. Most importantly, Zhang and colleagues assumed a rather restrictive time horizon of ten years.³¹⁸ In such a short time frame, differences in both effects and costs of the two studied treatments could not fully be captured. Assuming a similar time horizon in our study would also lead to an ICER above the assumed WTP-threshold.

Including future non-medical costs in a societal perspective

As described in **Chapter 1**, two main perspectives used in CUAs stand out: the healthcare perspective and the societal perspective.²¹ For either perspective, most pharmacoeconomic guidelines prefer a lifetime horizon on costs.²⁶ Consequently, the inclusion of future costs should be considered as well. A systematic review published in 2015, found that the number of publications to include future costs in general increased by 40% (to 70.8%) between 2008 and 2013.²⁷ While most of the studies detected (i.e. 49%) incorporated future medical costs related to the studied disease (also referred to as related future costs), only 4.2% included future medical costs not related to the studied disease (also referred to as future unrelated medical costs). None of the studies included in the review considered future non-medical (i.e. productivity or consumption) costs. A reason to not include the latter may be that most pharmacoeconomic guidelines do not yet explicitly mentioned their inclusion.^{26,27} Some guidelines (e.g. in the US) however already do so and it seems that the scientific debate on whether to include these costs settles in favour of the US approach.^{26,27,259,287} Regardless this ongoing debate, the impact of including future non-medical costs in CUAs remains understudied.^{26,27}

Both **Chapters 5 and 6** assessed the cost-utility of a novel treatment in haemato-oncology from a healthcare and a societal perspective. In addition, future non-medical costs were included to determine the impact of this component on the ICER. The inclusion of the latter costs was possible due to a recent update of the iMTA *Practical Application to Include Disease Costs* (PAID) tool.²⁷⁶ Hence, the studies presented in **Chapters 5 and 6** were the first to incorporate these costs in their assessment and can therefore be seen as case studies to examine the impact on the ICER when these costs are added to a societal perspective.

Including future non-medical consumption costs in a societal perspective, lead to an increase in the ICER between 17% and 21% in **Chapter 5**, when compared to the societal perspective alone. When future non-medical costs were included in a societal perspective in **Chapter 6**, the ICER increased by approximately 22% when compared to the societal perspective alone. However, despite these rather large increases in the ICER, the results of these two studies showed that considering future non-medical consumption costs within a societal perspective does not necessarily influence the decision to consider a treatment cost-effective. Whether or not this holds true for other studies as well depends on the modelled efficacy of a treatment, its costs, and the assumed WTP-threshold. When incremental effects (i.e. life years or QALYs) are relatively high for the novel treatment, considering

future non-medical costs might not influence a positive reimbursement (as seen in **Chapter 5**). However, when the ICER from a societal perspective is already close to the assumed WTP-threshold, considering future non-medical costs might lead to an ICER exceeding the WTP-threshold (as seen in **Chapter 6**).

It needs to be noted that especially the results of the study presented in **Chapter 5** are related to some uncertainty. Since the patient population of interest were children and young adults, the modelled time horizon was substantially longer when compared to patients included in **Chapter 6**. This not only introduces uncertainty in the modelling of long-term efficacy but also in modelling cost items such as productivity losses or gains. Typically, economic evaluations from a societal perspective consider future production costs. These are usually referred to as productivity losses when adults are the patient population of interest. When children and young adults are the patient group of interest however (as in **Chapter 5**), they are usually not yet part of the workforce and hence productivity *losses* cannot be considered. Instead, disease survivors might be able to work in the future. Hence productivity *gains* should be considered for this group. Modelling potential productivity gains in this population is challenging since little is known about both educational and employment prospects of long-term survivors of childhood cancer. Also, the estimation of potential productivity gains should account for future fluctuations on the job market for the jurisdiction of interest which introduces additional sources of uncertainty.

The decision as to whether or not future non-medical costs should be considered in economic evaluations should not be driven by the impact of these costs on the ICER. It is rather a fundamental methodological question within health economics that needs to be answered through scientific discourse. While this debate is currently ongoing, clear recommendations put forward through pharmacoeconomic guidelines have probably the biggest potential to resolve this uncertainty. The recommendations issued by the US *Second Panel on Cost Effectiveness in Health and Medicine* in 2018 were a first step in this direction.²⁸⁷ Whether other countries will follow is not yet clear. However, given the potential of exceeding the WTP-threshold when future non-medical costs are considered, their impact should at least be explored in sensitivity analyses of economic evaluation already now. Especially, since the recent update of the iMTA PAID tool facilitates the inclusion of these costs, at least for the Netherlands.²⁵⁹ Arguably, this tool should be extended to also include cost estimates from other countries to allow for a more seamless implementation in different jurisdictions. Efforts to do this are already underway as a recent publication of a separate PAID version to include future unrelated medical costs for economic evaluations in England and Wales show.⁴⁶² It is unfortunate that this version does not include future non-medical costs altogether.

The need for accurate health state utility values

Health state utility (HSU) values are an integral part of CUAs as they allow the calculation of quality-adjusted life years (QALYs). Since most contemporary clinical trials collect health-

related quality of life (HRQoL) data, they can be an important source for synthesising such evidence.⁴⁶³ Nevertheless, HSU values are regarded as one of the most uncertain input parameters of cost-utility models which simultaneously have the potential to heavily impact both accuracy and precision of the model results.⁴⁶⁴

Despite their relative importance to economic modelling studies, HSU estimates of haematological malignancies seem to be rarely reported in the literature. For the indication of FL for instance, utilities from a study of Wild et al.³⁴⁰ are commonly used for CUAs in this field.^{465–472} Similarly, studies examining HRQoL of patients diagnosed with multiple myeloma were found to be scarce.⁴⁷³

Results from the widely cited study of Wild et al.³⁴⁰ are only available in form of a conference abstract and therefore the employed methodology is not fully disclosed. For the study in **Chapter 6**, patient level HRQoL data were available and therefore HSUs for the economic model were estimated based on the most recent ISPOR guideline.⁴⁶⁴ Outcomes of this analysis suggested no statistically significant difference between either administered treatment in the clinical study. This was in line with the analysis of the same data conducted by the principle investigator of the trial.³⁰⁰ More importantly however, our analysis also did not find any differences in HRQoL between the health state of progression-free and progressive disease. This finding is at least counterintuitive as a recent cohort study including more than 2,000 patient with metastatic breast, pancreatic, lung, or colorectal cancer found that disease progression is related to worse outcomes in many HRQoL scales.⁴⁷⁴ It needs to be noted that this study did not include patients with haematological cancers, nor did the study include a generic HRQoL questionnaire such as the EQ-5D.²⁹⁹ For economic evaluations in healthcare, such generic questionnaires are generally preferred as they allow a comparison of outcomes across different diseases.¹⁹ Currently, a comprehensive overview relevant HSUs for haematological diseases is lacking. A systematic summary in the form a literature review could shed light on this. Alternatively, a cohort study including patients with haematological malignancies could reveal HSUs for this patient group. In this way, findings on the HSU used in **Chapter 6** could be validated.

PART III: IMPLICATIONS OF CUAs ON HEALTHCARE DECISION-MAKING

Implications of CUAs on reimbursement decisions in haemato-oncology

As stated in **Chapter 1**, economic evidence generated from CUAs can guide reimbursement decision-making in healthcare. In this dissertation, the policy implications were studied for the three CUAs described in **Chapters 5 to 7**. All three analyses assessed the cost-utility of novel, expensive treatments in haemato-oncology and provided the first economic evidence

on the treatment of interest for the pertinent jurisdiction. To understand the implications of the CUA results on policy and decision making, **Chapters 5 to 7** need to be interpreted in the context of the respective jurisdiction. While **Chapters 5 and 6** were conducted to primarily inform Dutch reimbursement decision, **Chapter 7** was performed for a UK perspective.

The relevance of CUAs when the estimated budget impact is low in the Netherlands

In the Netherlands, CUAs are required to inform reimbursement decisions for novel and expensive treatments. To keep the time between marketing authorization and the decision for reimbursement as short as possible, manufacturers often commission independent research institutes to perform the CUA for the eventual submission of evidence to the *National Health Care Institute* (Zorginstituut Nederland, ZIN). Studies presented in **Chapters 5 and 6** are both examples of this process as they were both submitted for the reimbursement decision process of the treatment studied. Nevertheless, results of neither Chapter seemed to have played a role in the decision to reimburse the novel treatment.

Despite its relatively high list price of 320,000 EUR per patient, the budget impact of tisagenlecleucel (**Chapter 5**) was seen as “low” and below the threshold that requires a full cost-effectiveness analysis. After all, the ZIN estimated that approximately 9 patients per year would receive the drug. When compared to the current standard treatment of blinatumomab, the ZIN estimated that this would lead to incremental costs of 2.1 million EUR per year, considering treatment, administration and monitoring costs. Nevertheless, results of **Chapter 8** show that these costs are likely to increase in the future due to an increase in eligible patients.

Although the Dutch EE guideline prefers discounted, societal costs from a lifetime perspective to support evidence-based decisions in healthcare,³¹⁴ the estimates from the budget impact analysis (BIA) for tisagenlecleucel only considered undiscounted direct medical healthcare costs for one year. Such an analysis neglects several aspects that are specific to CAR T-cell therapies and influence both costs and patient outcomes.

CAR T-cell therapy is a particularly complex treatment requiring an extraction of the patient’s own T cells.⁴⁷⁵ These cells are then transported to a specialised facility where they are genetically engineered to become CAR T-cells that target the desired cancer cells.⁴⁷⁶ After the CAR T-cells are amplified by several million-fold, they can be transfused back into the patient.⁴⁷⁷ This is a time consuming process with a median manufacturing time of 23 days (range, 21-37 days) from receipt of the material at the manufacturing facility to return to the clinical facility.⁴⁷⁸ It needs to be noted that these figures are only valid for US which holds at least two centralised manufacturing facilities.⁴⁷⁸ For the European market the first manufacturing facility is currently built in Switzerland and estimated to be functional by the year 2021.⁴⁷⁹ Until then, shipment of patients’ own T cell and CAR T-cells between

Europe and the US is necessary, adding to both costs and wait time. Only recently a study on the impact of increased wait times on overall mortality of CAR T-cells in large B-cell lymphoma (DLBCL) found that even a modest delay in the therapy significantly impacts its effectiveness negatively.⁴⁰⁹ There is little reason to believe that this impact might be different in other indications. In addition to the high costs of pre- and post-treatment, some patient might not survive such wait times and die before receiving the final product. All such (potential) negative impacts on both effect and costs of the novel treatment were not and cannot be considered in a BIA and hence its value of information to the reimbursement decision can be questioned.

In a similar case, the results of the CUA presented in **Chapter 6** showed a considerable level of uncertainty of the novel treatment (R-LEN) being cost-effective in a Dutch setting. Nevertheless, the Dutch Minister of Health described the reimbursement negotiations with the manufacturer as an “exceptional” case, for which the ZIN was not asked for advice.³²¹ He argued that the treatment was originally placed in the lock due expected high costs for the treatment of another indication (multiple myeloma). Once in the lock, the treatment would automatically be exempted from the basic insurance package for all new indications. For the recent extension of marketing authorisation, a previously conducted horizon scan of the ZIN had expected no more than 10 to 15 patients on a yearly basis for the indication at hand.³²¹ Therefore, total healthcare costs for the new indication were expected to not exceed the amount of 1 million EUR per year.³²¹ Specifics of this calculation were not disclosed but it can be assumed that these estimates were based on a BIA.

Although the budget impact for novel treatments studied in **Chapters 5 and 6** were seen as too low to require a full HTA for the reimbursement assessment by the Dutch authorities, it needs to be noted that both treatments currently have marketing authorisation for several indications in the EU. Tisagenlecleucel (**Chapter 5**) holds central marketing authorisation by the EMA for children and young adults with B-cell acute lymphoblastic leukaemia (pALL), and diffuse large B-cell lymphoma (DLBCL).⁵⁰ Lenalidomide (**Chapter 6**) is authorised by the EMA for the treatment of multiple myeloma, myelodysplastic syndrome, mantle cell lymphoma, and FL.⁴⁸⁰ And although the argumentation of a “low budget impact” might hold true when considering one particular indication, the budgetary implications for these two treatments across all indications might differ significantly. Indeed, the results of **Chapter 8** show that the costs for CAR T-cell therapy alone could be as high as 54.5 million EUR for the treatment of patients with pALL and DLBCL in the Netherlands in 2020. Similarly, a recently published investigation showed that lenalidomide alone generates a global annual revenue of approximately 6.2 million EUR, making it the most successful treatment in terms of total revenue.⁴⁸¹

While BIAs can inform reimbursement decisions, they are also associated with considerable uncertainty.⁴⁸² Due to limited data availability for most input parameters, standard methods used in economic evaluations such as one-way or probabilistic sensitivity analyses

cannot be conducted.⁴⁸³ A systematic review of BIAs on pharmaceutical drugs in the EU found that most of these analyses were conducted with poor methodological quality.⁴⁸⁴ In addition, 76% of the BIAs considered were not accompanied by a full economic evaluation.⁴⁸⁴ Another review of BIAs for the US market found that the ratio of predicted versus actual budget impact ranged between 0.2 and 37.5 with a mean value of 5.5.⁴⁸⁵

Admittedly, for the particular case of tisagenlecleucel, outcomes of the economic evaluation in **Chapter 5** and results from the BIA would essentially lead to the same positive recommendation to reimburse tisagenlecleucel. However, this is not necessarily the case for **Chapter 6**, as the probability of R-LEN being cost-effective heavily depends on the chosen perspective and the several other assumptions.

Basing reimbursement decisions of novel and expensive treatment options on BIAs alone may be a way to quickly derive conclusions. Nevertheless, such an approach does not allow for optimal resource allocation or to generate evidence on the health gains of a particular intervention. In 2015, the ZIN warned that if no such information was gathered, “society may end up spending money on interventions that result in relatively few health gains for patients”.⁴⁸⁶ Using information from BIAs to derive reimbursement decisions undermines the goal to derive such decisions on the basis of a solid evidence-based framework. CUAs *per contra* are better suited to support such decisions.

The impact of immature RCT data on reimbursement decisions

Chapter 7 demonstrated that, in the case of immature RCT data, reimbursement decisions can become increasingly uncertain. Although the estimated ICER in the study presented in **Chapter 7** was below a WTP-threshold of 30,000 GBP/QALY gained, the NICE appraisal committee initially issued a negative reimbursement decision. This was because the committee found that the estimates of the cost-utility analysis were not robust enough, due to the immaturity of the clinical trial data. After narrowing down the patient population and providing a higher financial discount on the price for the intervention, the degree of decision uncertainty was reduced to an extent that the appraisal committee could issue a positive recommendation. This demonstrates that the choice of the patient population is of crucial importance to determine whether a treatment should be reimbursed. This finding correlates with the issues of *post hoc* subgroup analysis discussed earlier in this chapter. Hence, involving reimbursement authorities early in the discussion of which subgroups are of eventual interest for reimbursing novel treatments might help in setting-up RCTs with relevant subgroups.

The financial impact of novel immunotherapies in haemato-oncology

The chimeric antigen receptor (CAR) technology is seen a biologically and economically powerful tool.⁴⁸⁷ Biologically powerful because CAR T cell therapy has been able to cure cancer in some patients for whom chemotherapy had failed.⁴⁸⁷ Economically powerful because the CAR T cell therapy tisagenlecleucel was considered the most expensive oncological

therapy available at the time of its marketing approval by the US *Food and Drug Administration* (FDA) in 2017.^{451,488}

Based on HTA evidence, all countries of the former EU-5 have adopted outcomes-based reimbursement scheme to safeguard patients' access to the therapy.⁴⁰⁷ As mentioned earlier, in the Netherlands, "standard reimbursement" was negotiated on the basis of a BIA.

Nonetheless, the *European Haematology Association* (EHA) was concerned about the sustainability of the pricing of novel oncological treatments in haematology. Especially, since CAR T-cell therapies can be used to treat many more haematological malignancies than the ones for which they currently hold market approval (i.e. ALL and DLBCL). The potential financial impact of this therapy on European health systems was unknown, and **Chapter 8** aimed to shed light on this issue.

Based on ongoing clinical studies, it was estimated that the use for CAR T-cell therapies might be expanded to include other haematological indications such as mantle cell lymphoma (MCL), FL, acute myeloid leukemia (AML), multiple myeloma (MM), and lymphocytic leukemia (CLL). **Chapter 8** found that the future cost of CAR T-cell therapies in the field of haematology will be substantial and increasing. This increase will not only be caused by an extension of indication but also because the underlying population forecasts predicted an increase in the eligible patient population. Population growth and an increase in (haematological) cancer incidences were drivers for this trend. In addition, CAR T-cell therapies were approved only for third or later treatment lines. The aim of several RCTs was to determine the use of this therapy in second-line treatment.⁴⁸⁹ If this proves to be effective, the eligible patient population might once more increase drastically. Consequently, the healthcare costs associated with CAR T-cell therapies will again increase.

These findings indicate that the trend of increasing costs of cancer treatments (introduced in the **Chapter 1**), is unlikely to be a temporary phenomenon. Indeed, novel cancer treatments such as CAR T-cell therapies showed to demand prices that were unheard of a couple of years before their introduction. With an extension of indication and a growing cancer incidence, healthcare systems might soon not be able to afford any novel treatments. Paired with unequal access to novel treatments that lead to tremendous losses of life years in itself,⁴⁹⁰ this trend can have devastating effects on the health of populations.

Decision makers have several tools at their disposal to control prices of medical treatments such as value-based pricing through HTA. This dissertation identified and addressed some of the current challenges researchers and reimbursement decision makers face when conducting or interpreting economic evaluations as part of formal HTA. Ultimately, it is in the hand of the decision makers whether or not economic evaluations should be used to decide on the reimbursement of novel and expensive treatments in haemato-oncology.

CONCLUDING REMARKS & RECOMMENDATIONS

The aim of this dissertation was threefold. First, challenges in the evidence synthesis for HTA were explored and addressed. Second, the cost-utility of novel and expensive treatments in the field of haemato-oncology was assessed. Third, several implications of CUAs on the healthcare decision-making were discussed.

More specifically, in the first part of this dissertation the current challenge of finding previously published economic evaluations was addressed by proposing a practical guidance aiding in systematically searching biomedical databases for such studies. In addition, several challenges were identified in synthesising evidence on effects of clinical studies, and evidence on costs from financial claims databases. The second part presented missing evidence on the cost-utility of two novel treatments in haemato-oncology and discussed the inclusion of future non-medical costs in a societal perspective of CUAs and the choice of health state utilities for these analyses. Finally, the third part placed the findings of the two CUAs of the second part into the context of healthcare decision making and provided an outlook on future healthcare expenditure in the field of haemato-oncology.

The findings of this dissertation lead to several implications and recommendations that are listed and explained below. It needs to be noted that the identified challenges in this dissertation do not represent an exhaustive list of all possible challenges in HTA. Nor are the here examined domains the sole domains of HTA. The following implications and recommendations should therefore be read in this context. In addition, their order does not reflect preference.

One, future research should aim at enhancing and updating current guidelines to conduct systematic literature reviews of economic evaluations, taking into account improved and simplified user interfaces of biomedical databases. Simultaneously, novel approaches such as a machine learning algorithm should be studied for their suitability to automate (parts of) such reviews. In case such tools are deemed appropriate their use should actively be recommended in up-to-date guidelines.

Two, future research needs to validate promising novel modelling techniques to extrapolate short-term empirical survival of clinical studies to a longer time horizon while considering external long-term data.

Three, results from cost-utility analyses that were based on efficacy data from phase II clinical studies need to be validated with long-term efficacy data from pivotal trials. Furthermore, clinical studies to collect the needed data should become mandatory when reimbursement decisions are based in phase II studies to reduce long-term uncertainties of the reimbursement decision.

Four, future research should determine strengths and weaknesses of synthesising evidence on resource use from financial claims databases compared to patient questionnaires. In addi-

tion, such research should elucidate the possibilities to enhance financial claims databases in a way so that they are better suitable for scientific research.

Five, national pharmacoeconomic guidelines should be updated to specifically recommend or discourage the inclusion of future non-medical costs in CUAs. It seems that the literature has a preference for including such costs since only then estimates from a societal perspective are complete. However, a lack in recommendations from said guidelines did not encourage their inclusion thus far. Clear recommendations such as in the US would help to generate comprehensive results from a societal perspective while ensuring a relative degree of comparability between studies that include such costs.

Six, future research should establish reliable methods to estimate potential future productivity gains for children and young adult cancer survivors. This is because CUAs typically consider future effects (e.g. long-term survival and HRQoL). Consequently, future costs such as those related to productivity, should be considered as well. While standard methodological approaches to include productivity losses are well documented in the literature, similar techniques are lacking to estimate productivity gains of young cancer survivors. This is problematic because other than adult patients, paediatric and young adult patients do not usually incur productivity losses due to their age. Hence future cost estimates in this young group of patients are often incomplete.

Seven, further research is needed to determine reliable estimates of health state utility values for patients with haematological malignancies. A systematic literature review in this field could help to summarise available evidence and to identify gaps.

Eight, the use of budget impact analyses to guide reimbursement decision in healthcare, especially in the field of haemato-oncology should be reconsidered. Other than budget impact analyses, economic evaluations can address a broad range of uncertainty and should therefore be seen as the superior methodology to address the reimbursement decision problem.

In essence, this dissertation adds to the growing body of literature aiming at updating and enhancing (methods of) economic evaluations through identifying and addressing challenges in HTA, to make them an even more robust and reliable tool in assessing the value of novel treatments.

Summary

Recent advances in the treatment of haematological cancers promise to further improve treatment outcomes for patients. Simultaneously, prices of these treatments are high and continuously increasing since a couple of decades. While improved treatment outcomes are desirable, the continuous price increase of novel and high budget impact therapies has become a major topic for decision makers in healthcare. Determining drug prices of novel treatments based on their value perceived by patients and healthcare decision makers is one approach to control the increasing treatment prices. Through a formal health technology assessment (HTA) this value can be determined. This is typically done by systematically evaluating the clinical, economic, organisational, social and ethical aspects of the novel treatment. Although the concept of HTA is already in use since the 1980's, various challenges persist to this day. This dissertation identifies and addresses some of these challenges and is structured in three parts. In the first part, current challenges in the evidence synthesis for HTA are explored and addressed. The second part aims at providing missing evidence on the cost-utility of novel and expensive treatments in the field of haemato-oncology. Simultaneously, it is explored to what extent the inclusion of future non-medical consumption costs impact the ICER of cost-utility analyses. Finally, implications of cost-utility analyses (CUAs) on healthcare decision-making are described and discussed in the third part.

Part I: Challenges in the evidence synthesis for Health Technology Assessment

For a formal HTA, previously published economic evidence on the treatment of interest needs to be reviewed systematically. However, searching and finding economic evaluation studies in general has become challenging since previous economic evaluation databases are no longer updated or discontinued. **Chapter 2** addresses this challenge by proposing a guideline to identify such studies in a systematic way. The recommendations include searching at least five "basic" databases using validated search filters with minimal restrictions. In addition, the retrieved references should be independently screened by two reviewers and a biomedical information specialist should be consulted for the entire process. These recommendations were recently adopted by WHO-INTEGRATE (INTEGRATE Evidence) framework version 1.0 to gather economic evidence in health decision making.

Chapter 3 identifies challenges in synthesising evidence on costs. Using two distinct approaches, healthcare costs of paediatric patients with sickle cell disease were estimated. One approach used the current Dutch clinical practice guideline for the treatment of paediatric patients with sickle cell disease. For the other approach, healthcare costs were estimated using a hospital financial claims database. Estimating healthcare costs with the former approach was feasible and relatively uncomplicated. However, real-world resource use could not be included. Using financial claims data, did offer a detailed insight into real-world resource use but was related to some specific challenges. Some of these challenges included the suitability of the available variables for the desired analyses as well as limited access to the database for

research purposes. In total, 125 patients could be included for the analysis. Of those, 15% were responsible for 50% of the total healthcare costs. Inpatient hospital care was the main cost driver, followed by diagnostics, treatment, outpatient visits and emergency care. The yearly average healthcare expenditures for this patient group were 5,049 EUR per patient (SD: 1,634 EUR) but varied considerably between the different age groups analysed. From this chapter it could be concluded that hospital financial claims data can be used for the estimation of real-world healthcare costs. Nevertheless, future research needs to determine the usefulness of such an approach in other disease contexts.

One aim of the European Medicine Agency (EMA) is to ensure the timely access for patients to treatments targeting an unmet medical need. Ideally, phase III clinical data are used for such purposes. However, the completion of such studies is time consuming. Therefore, the EMA has increasingly issued marketing approval based on phase II clinical studies in recent years. **Chapter 4** explores the usefulness of phase II clinical data to develop a decision model for health economic modelling purposes and to estimate long-term survival outcomes. It describes the development of a decision model for the second-line treatment of steroid-refractory acute graft-versus-host disease (SR-aGvHD) with mesenchymal stromal cells (MSCs). The model was developed in conjunction with a group of international clinical experts and consisted of eight health states. In addition, published (anonymised) patient-level evidence from several phase II studies were used to estimate long-term efficacy outcomes. In total, data from 327 paediatric and adult patients with SR-aGvHD could be used to estimate long-term overall survival (OS). Patients in complete remission after MSCs had a median OS of 3.2 years while patients with no complete remission reached a median OS of 0.5 years. Nevertheless, the results of this analysis need to be interpreted as an *indication* for the studied patient population and data from phase III clinical trials need to validate these findings.

PART II: Cost-utility of novel treatments in haematology-oncology

In **Chapter 5**, the cost-effectiveness of the chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel is assessed for pediatric patients with relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL) in the Netherlands. Comparator treatments were clofarabine monotherapy (Clo-M), clofarabine combination therapy (Clo-C), and blinatumomab (Blina). The analysis was conducted from societal perspective and in a separate scenario, future non-medical consumption costs were considered as well. The estimated ICERs ranged between 31,682 EUR per quality-adjusted life year (QALY) and 37,531 EUR per QALY when tisagenlecleucel was compared to Blina and Clo-C, respectively. Including future non-medical costs in a societal perspective lead to increase in the estimated ICER between 17% and 21% when compared to a societal perspective that did not include these costs. With a willingness-to-pay (WTP) threshold of 80,000 EUR per QALY gained, tisagenlecleucel was cost-effective compared to each of the comparators, and from all perspectives.

In **Chapter 6**, the cost-effectiveness of rituximab plus lenalidomide (R-LEN) for previously treated patients with follicular lymphoma (FL) in the Netherlands is estimated. Similar to Chapter 5, this Chapter also includes a separate analysis considering future non-medical costs. With a WTP-threshold of 50,000 EUR per QALY gained, R-LEN was cost-effective with an ICER of 40,493 EUR per QALY from a societal perspective when compared to R-mono. When future non-medical costs were considered as well, the ICER increased by approximately 22%.

Chapter 5 and 6 demonstrate that the studied treatments are expensive, but also cost-effective from all perspectives and when compared to each comparator treatment. When future non-medical costs were considered in the analyses, the ICER became less favourable. Nevertheless, the conclusion as to whether the treatments could be considered cost-effective did not change.

PART III: Implications of cost-utility analyses of novel and expensive treatments in haemato-oncology on healthcare decision-making

Chapter 7 elicits the review process of a single technology appraisal (obinutuzumab in combination with chemotherapy) to the *National Institute for Health and Care Excellence* (NICE). The ICER estimated through the underlying CUA was below the assumed WTP-threshold. Nevertheless, the appraisal committee issued a negative reimbursement recommendation for the treatment. This decision was based on the limited follow-up time of the clinical study used for the economic evaluation. After considering only a patient subgroup with high disease severity and granting a (confidential) price discount, the appraisal committee issued a positive reimbursement recommendation for the drug.

In recent years, novel and expensive anti-cancer therapies such as the CAR technology have sparked a debate about the costs of such therapies and the affordability of healthcare systems globally. In addition, there is growing concern about the sustainability of the pricing of novel oncological treatment in haematology. **Chapter 8** assessed the health economic aspects of CAR T-cell therapies for haematological cancers for the former EU-5 and the Netherlands. Average cumulative expenditures across both existing and future indications for the years 2019 to 2029 were estimated to be 28.5 billion EUR, 32.8 billion EUR, and 28.9 billion EUR, when considering costs of CAR T-cell therapy only, CAR T-cell therapy including pre- and post-treatment, and incremental CAR T-cell therapy cost, respectively. It was concluded that healthcare costs associated with this novel therapy are considerable and increasing in the near future.

This dissertation explores and addresses several challenges in the evidence synthesis for HTA, assesses the cost-utility of two novel and expensive haemato-oncological treatments, and discusses the implications of CUAs on the healthcare decision-making processes. While novel and expensive haemato-oncological treatments bear the potential to cure a group of patients, they also put the affordability of healthcare systems at risk. HTA, much more than

budget impact analyses can help to keep determining and control spiralling drug prices. However, it can also be concluded that methodological choices and unsolved challenges in HTA have a substantial impact on economic evaluations and reimbursement decisions. Ultimately, this dissertation adds to the growing body of literature aiming at updating and enhancing (methods of) economic evaluations through identifying and addressing challenges in HTA, to make them an even more robust and reliable tool in assessing the value of novel treatments.

Nederlandse samenvatting

De nieuwste ontwikkelingen op het gebied van hematologische kankerbehandelingen zijn veelbelovend voor jonge en oudere patiënten. Tegelijkertijd zijn de prijzen van deze behandelingen hoog en stijgen ze al sinds enkele decennia. Hoewel verbeterde behandelresultaten wenselijk zijn, is de voortdurende prijsstijging van nieuwe therapieën met een hoge budgetimpact een cruciaal onderwerp geworden voor beleidsmakers in de gezondheidszorg. Een manier om deze stijgende prijzen tegen te gaan is om medicijnprijzen op basis van de toegevoegde waarde voor patiënten en beleidsmakers te bepalen. Dit kan bijvoorbeeld door middel van een formele beoordeling van gezondheidstechnologie (Health Technology Assessment, HTA), waarbij kosten en baten (bijvoorbeeld klinische, economische, organisatorische, sociale en ethische aspecten) van de nieuwe behandeling systematisch onderzocht worden. Hoewel het concept van HTA al sinds de jaren 1980 in gebruik is, bestaan er nog steeds verschillende (methodologische) uitdagingen. Dit proefschrift identificeert en behandelt enkele van deze uitdagingen om het veld van HTA te verrijken. Hiervoor is het proefschrift gestructureerd in drie delen. In het eerste deel worden huidige uitdagingen in het combineren van bewijs voor HTA geadresseerd. Deel twee is gericht op het leveren van ontbrekend bewijs over de kosten-uiteitheid van nieuwe en dure behandelingen op het gebied van hemato-oncologie. Tegelijkertijd wordt er bestudeerd in hoeverre het meenemen van toekomstige niet-medische consumptiekosten de uitkomsten van kostenutiliteitsanalyses (KUAs) beïnvloedt. Tenslotte worden de implicaties van KUAs op de besluitvorming in de gezondheidszorg werden beschreven en besproken in het derde deel van dit proefschrift.

DEEL I: UITDAGINGEN IN DE SYNTHESE VAN BEWIJS VOOR HEALTH TECHNOLOGY ASSESSMENT

Voor een formeel HTA moet eerder gepubliceerd economisch bewijs over de behandeling systematisch worden herzien. Het zoeken en vinden van economische evaluatiestudies in het algemeen is echter een uitdaging geworden, aangezien eerdere databases voor economische evaluatie niet langer worden bijgewerkt of zijn beëindigd. **Hoofdstuk 2** gaat in op deze uitdaging en stelt een richtlijn voor om dergelijke studies op een systematische manier te identificeren. De aanbevelingen omvatten het gebruiken van ten minste vijf “basis” databanken met gevalideerde zoekfilters. Bovendien wordt aanbevolen om de opgehaalde referenties door twee auteurs onafhankelijk te screenen en om een biomedische informatiespecialist te betrekken. Deze aanbevelingen zijn onlangs overgenomen door de WHO-INTEGRATE (INTEGRATe Evidence) framework versie 1.0 om economisch bewijs te verzamelen om besluitvorming voor de gezondheidszorg te informeren.

Hoofdstuk 3 identificeert uitdagingen gerelateerd aan het synthetiseren van bewijs over kosten. Met behulp van twee verschillende methoden werden de zorgkosten van pediatrie patiënten met sikkelcelziekte geschat. Enerzijds werd de huidige Nederlandse richtlijn

voor de behandeling van pediatrische patiënten met sikkelcelziekte gebruikt. Anderzijds werden de zorgkosten geschat met behulp van een database met de financiële claims van ziekenhuizen. Hoewel het schatten van de zorgkosten met de eerste benadering haalbaar en relatief eenvoudig was, was dit niet representatief voor het daadwerkelijke zorggebruik van patiënten. Het gebruik van een financiële databank voor dit doel bood weliswaar een meer gedetailleerd inzicht in het zorggebruik van patiënten, maar kende ook specifieke uitdagingen. Bijvoorbeeld de geschiktheid van de beschikbare variabelen voor de analyses en een beperkte toegang tot de database voor onderzoeksdoeleinden. Uiteindelijk werden 125 patiënten geïnccludeerd voor de analyse waarvan 15% van de patiënten verantwoordelijk was voor 50% van de totale zorgkosten. Intramurale ziekenhuiszorg was de belangrijkste kostenfactor, gevolgd van diagnostiek, behandeling, poliklinische bezoeken en spoedeisende zorg. De gemiddelde jaarlijkse uitgaven voor de gezondheidszorg van deze patiëntengroep bedroeg 5.049 EUR per patiënt (SD: 1.634 EUR), maar varieerden aanzienlijk tussen de verschillende geanalyseerde leeftijdsgroepen. Op basis van de inzichten uit dit hoofdstuk kan worden geconcludeerd dat het mogelijk is om financiële claims data van ziekenhuizen te gebruiken voor het schatten van daadwerkelijke zorgkosten. Toekomstig onderzoek moet uitwijzen of deze methode in vergelijking met andere bronnen, ook in een andere ziektecontext mogelijk is.

Een van de doelstellingen van het Europees Geneesmiddelenbureau (European Medicines Agency, EMA) is om ervoor te zorgen dat patiënten tijdig toegang krijgen tot behandelingen die gericht zijn op een onvervulde medische behoefte. Idealiter wordt data uit fase III klinische studies voor dergelijke doeleinden gebruikt. Echter kosten dergelijke onderzoeken kost echter veel tijd. Om deze reden heeft de EMA in de afgelopen jaren markttoelatingen in toenemende mate gebaseerd op data van fase II studies. In reactie hierop wordt in **Hoofdstuk 4** de mogelijkheid onderzocht om data uit fase II studies te gebruiken om een beslismodel te ontwikkelen dat gebruikt kan worden om lange termijn overleving en gezondheids-economische uitkomsten te voorspellen. Dit hoofdstuk beschrijft de ontwikkeling van een beslismodel voor de tweedelijsbehandeling van steroid-refractaire acute graft-versus-host-ziekte (SR-aGvHD) met mesenchymale stromale cellen (MSC's). Het model is ontwikkeld in samenwerking met een groep internationale klinische experts en bestaat uit acht gezondheidstoestanden. Daarbij is openbaar beschikbare (geanonimiseerde) data op patiëntniveau uit verschillende fase II-onderzoeken gebruikt om de effectiviteit op de lange termijn te schatten. In totaal zijn de gegevens van 327 pediatrische en volwassen patiënten met SR-aGvHD gebruikt om de algehele overleving op de lange termijn (overall survival, OS) te schatten. Patiënten in complete remissie na MSC's hadden een mediaan OS van 3,2 jaar terwijl patiënten zonder volledige remissie een mediane OS van 0,5 jaar bereikten. Desalniettemin moeten de resultaten van deze analyse geïnterpreteerd worden als een *indicatie* en moeten gegevens uit fase III klinische onderzoeken deze bevindingen volledig valideren.

DEEL II: KOSTEN-UTILITEIT VAN NIEUWE BEHANDELINGEN IN DE HEMATOLOGIE-ONCOLOGIE

In **Hoofdstuk 5** wordt de kosteneffectiviteit van de chimere antigeenreceptor (CAR) T-celtherapie tisagenlecleucel beoordeeld voor pediatrische patiënten met recidiverende of refractaire (r/r) acute lymfatische leukemie (ALL) in Nederland. Andere vergelijkende behandelingen waren clofarabine monotherapie (Clo-M), clofarabine combinatietherapie (Clo-C) en blinatumomab (Blina). De analyse is uitgevoerd vanuit het maatschappelijk perspectief. In een apart scenario worden ook toekomstige niet-medische consumptiekosten meegenomen. De geschatte ICER's varieerden tussen 31.682 EUR per kwaliteit gecorrigeerd levensjaar (quality-adjusted life year, QALY) en 37.531 EUR per QALY wanneer tisagenlecleucel werd vergeleken met respectievelijk Blina en Clo-C. Het meenemen van toekomstige niet-medische kosten in een maatschappelijk perspectief leidde tot een toename van de geschatte ICER tussen de 17% en 21% vergeleken met een maatschappelijk perspectief waarin deze kosten niet zijn meegenomen. Met een drempelwaarde van 80.000 EUR per gewonnen QALY, was tisagenlecleucel kosteneffectief in vergelijking met elk andere bestudeerde behandeling, en vanuit alle perspectieven.

In **Hoofdstuk 6** is de kosteneffectiviteit van rituximab plus lenalidomide (R-LEN) voor eerder behandelde patiënten met folliculair lymfoom (FL) in Nederland geschat. Net als in hoofdstuk 5, bevat dit hoofdstuk ook een afzonderlijke analyse waarin toekomstige niet-medische kosten zijn meegenomen. Met een WTP-drempel van 50.0000 EUR per gewonnen QALY, was R-LEN kosteneffectief met een ICER van 40,493 EUR per QALY vanuit een maatschappelijk perspectief in vergelijking met R-mono. Wanneer ook rekening werd gehouden met toekomstige niet-medische kosten, steeg de ICER met zo'n 22%.

Hoofdstuk 5 en 6 tonen aan dat de bestudeerde behandelingen duur maar ook kosteneffectief zijn vanuit alle perspectieven en vergeleken met elke vergelijkende behandeling. Wanneer toekomstige niet-medische kosten mee worden genomen in de analyse, werd de ICER minder gunstig. Desalniettemin veranderde de conclusie of de behandelingen als kosteneffectief kan worden beschouwd niet.

DEEL III: IMPLICATIES VAN KOSTENUTILITEITSANALYSES VAN NIEUWE EN DURE BEHANDELINGEN IN DE HEMATO-ONCOLOGIE VOOR DE BESLUITVORMING IN DE GEZONDHEIDSZORG

Hoofdstuk 7 beschrijft het beoordelingsproces van een nieuwe therapie (obinutuzumab in combinatie met chemotherapie) door het *National Institute for Health and Care Excellence* (NICE). De geschatte ICER lag onder de aangenomen WTP-drempel. Desondanks bracht de beoordelingscommissie een negatief vergoedingsadvies voor de behandeling uit. Deze beslissing was gebaseerd op de beperkte follow-up tijd van de klinische studie die werd gebruikt voor de economische evaluatie. Na alleen een subgroep van patiënten met een hoge ernst van ziekte te hebben overwogen en een (vertrouwelijke) prijskorting te hebben verleend, heeft de beoordelingscommissie het advies gegeven om het geneesmiddel te vergoeden.

In de afgelopen jaren hebben nieuwe en dure therapieën voor kanker, zoals de CAR-technologie, tot een debat geleid over de kosten van dergelijke therapieën en de betaalbaarheid van gezondheidszorgsystemen wereldwijd. Bovendien is er een groeiende bezorgdheid over de duurzaamheid van de prijsstelling van nieuwe oncologische behandelingen in de hematologie. In **Hoofdstuk 8** zijn de gezondheidseconomische aspecten van CAR T-celtherapieën voor hematologische kankers voor de voormalige EU-5 en Nederland onderzocht. De gemiddelde cumulatieve uitgaven voor zowel bestaande als toekomstige indicaties voor de jaren 2019 tot 2029 werden geschat op 28,5 miljard EUR, 32,8 miljard EUR en 28,9 miljard EUR, rekening houdend met de kosten van alleen CAR T-celtherapie, CAR T-celtherapie inclusief pre- en post-behandeling, en incrementele CAR T-celtherapie kosten, respectievelijk. Er is geconcludeerd dat de kosten van de gezondheidszorg in verband met deze nieuwe therapie aanzienlijk zijn en in de nabije toekomst verder zullen toenemen.

In dit proefschrift zijn verschillende uitdagingen in de synthese van bewijs voor HTA onderzocht, de kosten-utiliteit van twee nieuwe en dure hemato-oncologische behandelingen beoordeeld, en de implicaties van KUA's op de besluitvormingsprocessen in de gezondheidszorg besproken. Hoewel nieuwe en dure hemato-oncologische behandelingen het potentieel hebben om een groep patiënten te genezen, zetten ze ook de betaalbaarheid van zorgstelsels onder druk. HTA, veel meer dan budgetimpactanalyses, kan helpen om de stijgende medicijnprijzen te bepalen en te beheersen. Er kan echter ook worden geconcludeerd dat methodologische keuzes en onopgeloste uitdagingen in HTA een substantiële impact hebben op de uitkomsten van economische evaluaties en op vergoedingsbeslissingen. Uiteindelijk draagt dit proefschrift bij aan de groeiende hoeveelheid literatuur die gericht is op het actualiseren en verbeteren van (methoden van) economische evaluaties door het identificeren en aanpakken van uitdagingen in HTA, om ze een nog robuuster en betrouwbaarder instrument te maken voor het beoordelen van de waarde van nieuwe behandelingen.

PhD portfolio

PhD candidate	Wilhelm Frederick Thielen
Doctoral supervisor	Carin A. Uyl-de Groot
Daily advisor	Hedwig M. Blommestein
PhD period	September 2015 – December 2020

	Year	ECTS
Training activities		
<i>Courses & Workshops</i>		
• How to use EndNote	2015	0.1
• Systematic literature retrieval in PubMed, part I	2015	0.1
• Systematic literature retrieval in PubMed, part II	2015	0.1
• Systematic literature retrieval in other databases	2015	0.1
• Academic Integrity Day (Master Class)	2015	0.4
• Cost-effectiveness Analysis Alongside Clinical Trials (ISPOR)	2015	0.2
• Bayesian Analysis - Overview and Applications (ISPOR)	2015	0.4
• R Programming (online)	2016	2.0
• Network Meta-Analysis in Relative Effectiveness Research (ISPOR)	2016	0.2
• Decision modeling using R	2017	1.0
• Basic didactics & course dynamics		0.8
• Career guidance	2020	0.3
• Seminars & lectures		
• Workshop given: “How to incorporate economic evaluations in clinical practice guidelines: a practical workshop on research” (ISPOR)	2016	0.2
• Workshop given: “How to incorporate economic evaluations in clinical practice guidelines: a practical workshop on research” (Maastricht University)	2018	0.4
<i>Symposia & congresses</i>		
• ISPOR 18th Annual European Congres	2015	1.0
• ISPOR 19th Annual European Congres	2016	1.0
• Junior Researcher Programme (JRP) conference	2016	1.0
• lolaHESG	2016	1.0
• Organising committee of lolaHESG	2017	2.0
• ISPOR 20th Annual European Congres	2017	1.0
<i>Other</i>		
• Member “Jonge Zorgdenktank”	2016-2020	2.2
• Reviewer for scientific publication (1)	2016	0.1
• Reviewer for scientific publication (1)	2017	0.1
• Reviewer for scientific publications (2)	2018	0.2
• Reviewer for scientific publication (1)	2019	0.1
• Teaching activities		
• Mentoring/tutoring		
• Introductie in de Gezondheidswetenschappen (Bachelor)	2015-2016	0.4

• Inleiding Methoden en Technieken (Bachelor)	2016-2017	0.4
• Inleiding Methoden en Technieken (Pre-Master)	2016-2017	0.4
• Health Technology Assessment - Economic evaluation and the context of health care systems	2016-2017	0.2
• Introductie in de Gezondheidswetenschappen (Bachelor)	2017-2018	0.4
• Inleiding Methoden en Technieken (Pre-Master)	2017-2018	0.4
• Kwantitatief Leeronderzoek (KLO)	2017-2018	0.6
• Health Technology Assessment (Master)	2017-2018	0.4
• Advanced Health Economic Modelling (Master)	2017-2018	0.4
• Hoe houden we de zorg betaalbaar?	2017-2018	0.2
• Pharmaceutical pricing and Market Access (Master)	2017-2018	0.4
• Health Technology Assessment (Master)	2018-2019	0.4
• Advanced Health Economic Modelling (Master)	2018-2019	0.4
• Health Technology Assessment (Master)	2018-2019	0.4
• Health Technology Assessment (Master)	2019-2020	0.4
• Health Technology Assessment (Master)	2019-2020	0.4
Teaching activities		
<i>Supervision</i>		
• Master thesis (2 students)	2015-2016	3.0
• Master thesis (2 students)	2016-2017	3.0
• Master thesis (3 students)	2017-2018	4.5
• Master thesis (3 students)	2018-2019	4.5
• Master thesis (1 student)	2019-2020	1.5
<i>Lecturing</i>		
• “Health sector costs” (Master level)	2018-2019	0.8
• “Quality of Life, Part A” (Master level)	2018-2019	0.8
• “Economic aspects and reimbursement considerations for the treatment of haematological cancers. The example of chimeric antigen receptor T-cell (CAR T) therapy in paediatric acute lymphoblastic leukaemia (pALL)” (Master level)	2019-2020	0.8
<i>(Co-)Coordinating</i>		
• Pharmaceutical Pricing and Market Access (Master elective)	2019-2020	2.0
TOTAL		43.1

List of publications

INCLUDED IN THIS DISSERTATION

Thielen FW, Mastrigt GV, Burgers LT, et al. How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3). *Expert Review of Pharmacoeconomics & Outcomes Research*. 2016;16(6):705-721. doi:10.1080/14737167.2016.1246962

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NOT INCLUDED IN THIS DISSERTATION

Thielen FW. Entering your heart: how barely tested medical innovations find their way into clinical practice. In: *Governance of Health Care Innovation. Excursions into Politics, Science and Citizenship*. Vol 2. ; 2016:19-40.

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Wijnen BFM, Thielen FW, Konings S, et al. Designing and Testing of a Health-Economic Markov Model for Prevention and Treatment of Early Psychosis. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2019;20(3):269-279. doi:10.1080/14737167.2019.1632194

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About the author

Frederick Thielen was born on 24 February 1986 in München, Germany. In April 2006, he started an apprenticeship at the University Hospital in Aachen (UKA) to become a Nurse. During this time, he was elected chairman of the young people and apprentice representation at the UKA. After his apprenticeship he worked as a Nurse at an internal medicine ward at the UKA and was elected as exempted member of the staff council. In 2010, he started his studies in European Public Health (Bachelor) at Maastricht University and successfully participated in the honours programme “Governance of Health Care Innovation”. His honours thesis won the European Inter-University Association on Society, Science and Technology (ESST) Award for Aspiring Undergraduates. For writing his Bachelor thesis, he went to RAND Europe in Cambridge, UK. Before continuing with a Research Master in Health Science at Maastricht University (2013), he worked as a Research Assistant at RAND Europe during the summer of 2013. Simultaneously, he acted as research team lead of the Global Health Access Policy project (GHAP), a long-term study in collaboration with RAND Europe, Maastricht University, as well as the Engineering Design Centre and the Policy Research Group at the University of Cambridge. During his Master, Frederick successfully participated in the PREMIUM honours programme at Maastricht University and wrote his final thesis at the Trimbos institute in Utrecht.

In 2015, he started as a PhD for the European Horizon 2020 research project RETHRIM, on the cost-effectiveness of mesenchymal stromal cells for the treatment of steroid-refractory acute graft-versus-host-disease. Next to his PhD, he is an active member of a think tank for young professionals in healthcare (“Jonge Zorgdenktank”) since 2016 and teaches statistical programming and data science in R at TriData in Utrecht since 2019.

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