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 pateints 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finding economic evaluation studies in general has become challenging since previous economic evaluation databases are no longer updated or discontinued.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-word 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 tisganelecleucel 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 50,0000 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.