Discussion
The aim of the present thesis was to assess the potential challenges when developing health economic models for chronic diseases for reimbursement purposes in Europe. The focus was to address the specific questions presented in the introduction concerning the following four topics i.e. (1) modelling approach of chronic diseases, (2) country adaptations, (3) model parameter estimation and (4) factors affecting local reimbursement decisions. The nine questions presented in the introduction regarding the first two topics are answered in this discussion based on chapters 2-5. Notably, the models in these chapters have been submitted to several EU health authorities and were also critically appraised by them, as well as being published in peer-reviewed international journals.\textsuperscript{[1-12]} The questions regarding model parameter estimations are addressed in the discussion based on chapters 2-7. The question regarding the predictive factors for reimbursement decisions is addressed based on the findings presented in chapter 8.

In the remainder of the discussion the nine questions presented in the introduction are discussed consecutively per topic. Subsequently, prior to the conclusion, two paragraphs are presented describing the use for EU HTA collaborations, and how new and improved modelling approaches can further optimize and guide clinical development for reimbursement purposes.

**Modelling approach**

Obviously, there is not one ideal modelling approach (i.e. decision tree, Markov model and or DES) for modelling chronic diseases for reimbursement purposes. All approaches have their specific pro’s and con’s and the choice depends on numerous factors summarized below.

Decision trees are not ideally suited for modelling chronic diseases because of the limited capability to include changes over time (e.g. in disease progression)\textsuperscript{[13]}, which is important in most chronic diseases.\textsuperscript{[14]} Although time can be included in decision tree models, decision trees then often become complicated ‘decision forests’. The Markov approach models events as transitions from one health state to another over time and as such it is better suited for modelling processes in chronic diseases than a decision tree approach.\textsuperscript{[13, 14]} However, if the history of patients becomes important for current transitions, Markov models also have limitations, as the number of health states required to capture time dependency in the disease processes might increase significantly. A micro-simulation model can address patient history easily and is therefore the most flexible modelling approach.\textsuperscript{[14, 15]}

There are however some drawbacks that need to be considered when building such a micro-simulation model for reimbursement purposes. The first is simulation time. Consider for instance a hypothetical product that recently received EMA approval and the pharmaceutical dossiers need to be submitted to several local reimbursement agencies within a short timeframe. This micro-simulation requires a substantial amount of computing power, time and also human resources to conduct the corresponding base-case, univariate, scenario
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and probabilistic sensitivity analyses (PSA) simultaneously. Moreover, it is not uncommon that during reimbursement submissions, when the analyses have already started, base-case settings of the model change. Efficient programming could avoid re-running all results due to these changes. However, sometimes, all analyses may need to be rerun with the micro-simulation, which can be very time consuming and therefore not ideal just prior to local reimbursement submissions. Ergo, from the viewpoint of science efficiently contributing to practice, access to drugs and patients’ needs, delays may be undesirable and flexible and timely modelling – though still of high scientific standards – is needed. Another problem with micro-simulation models for reimbursement purposes is the transparency of programming and use of the model for the health authorities that evaluate the reimbursement submission. Most health authorities have limited time to evaluate reimbursement submissions, including the actual model and the programming. Gaining a thorough understanding whether the model is sound and valid obviously requires time. The English health authorities face these issues to a lesser extent because, contrarily to other local EU health authorities such as those in the Netherlands. Notably, the English health authorities do not review the submitted models themselves, but outsource that to specialist university centers, whereas other EU-countries don’t. Therefore, from the pharmaceutical company’s perspective, developing these complex models and applying them outside England involves a risk as it might be difficult to find a programmer/health-economist in the health authorities who has experience with the context, the methodologies and the programming language. Notably, it is crucial that a good modeler understands the context of the disease on top of the content and the program code of the model. Indeed, in the Dutch context non-transparent modelling is an often heard criticism regarding submissions for reimbursement. Notably, this criticism may arise from complex modelling on one side and lack of experience on the other side.

Chapter 3, 4 and 5 present three models for different chronic diseases, i.e., schizophrenia, cardiovascular disease and multiple myeloma, respectively. Both Markov modelling and discrete event simulation (DES) micro-simulation approaches were used. For schizophrenia (chapter 3) it was concluded that a DES model (chapter 2 and 3) was best suited to accurately model the compliance benefits of long acting risperidone and to capture all of the relevant interdependencies, and different patient histories, in this chronic, highly heterogeneous disease. This was done despite the risk of authorities having issues with potentially complex DES modelling. In light of the newer guidelines for DES modelling approaches, the choice for DES still holds, due to the fact that what happens to a schizophrenic patient is affected by what happened to that patient before (i.e., memory is crucial). Regarding future research, at the time of developing the schizophrenia model, a number of parameter estimates were derived from expert opinion. In future updates of the model, ideally the estimates based on expert opinion would be replaced by data from pragmatic randomized trials or other real world studies. The most important parameter in that respect is long acting risperidone’s comparative relative effectiveness versus oral atypicals and long acting first generation antipsychotics. However, in case such real world data is not available for
one or more parameters, the expert elicitation should still be applied, ideally according to
techniques as proposed by O’Hagan of the university of Sheffield. This specific method
allows for elicitation of both the point estimate and the uncertainty surrounding the point
estimate provided by the experts.

For the cardiovascular model (chapter 4) a Markov model was chosen. The reason was
that a cardiovascular disease model requires some memory (patient history) as the risk of
a cardiovascular event depends on age and on the number of previously suffered events,
but limited memory. Notably, by limiting the number of subsequent cardiovascular events
to three and defining three tunnel states per event sufficient memory could be accounted
for still in the Markov structure, that is well recognized and understood by health authorities.
This avoids some of the practical drawbacks of micro-simulations. Since our publications,
ISPOR guidelines for this type of modelling have been developed. Our modelling
is in line with those guidelines. Contrarily to schizophrenia where patients may suffer
numerous psychotic episodes in a lifetime, in cardiovascular disease there are few patients
that suffer more than three consecutive MI’s or strokes in a lifetime. This limits the number
of event health states required in a cardiovascular model compared to a schizophrenia
model. The Markov model approach therefore seems still sufficient to capture the full course
of cardiovascular disease, while it avoids the disadvantages of complexity and potential
non-transparency of DES. Future research should also focus on applying formal calibration
techniques for parameter estimation as well as separate distinction of hemorrhagic and
non-hemorrhagic strokes as separate health states in the model.

For the multiple myeloma model (chapter 5), also a Markov structure was used, which
distinguishes the complete, partial and non-response health states in first, second, third and
later lines of treatment. In first line treatment, time spent in the complete response (CR),
partial response (PR), and no response (NR) health states were captured by parametric
survival curves that were implemented in the model. For second, third and later
treatment lines, exponential survival curves were used. However, in second and later lines
the transition probabilities to go from CR, PR and NR to next lines of treatment or death
might be time dependent and potentially better be modelled with parametric survival curves
to capture that patient history. This was not done in the current model. Such functionality
would require extensive memory and therefore a micro-simulation would likely be the more
appropriate structure. Whilst this may provide more accuracy in the model predictions, the
gain in accuracy was outweighed by the practical disadvantages of a micro-simulation at this
stage. However, in the future it is likely that a micro-simulation will be built when trying to
capture all subtleties with respect to sequencing, which does however require a lot of specific
data. Regarding the underlying data of the model, in the current multiple myeloma model,
the main driver differentiating treatments was response (CR, PR and NR). Response came
forward as such in extensive discussions with clinicians, as achieving a complete response is
an important treatment goal in multiple myeloma. From a modelling perspective though,
progression free survival might be the stronger end-point and therefore preferred. At the time
of building the model, no data was available for most treatments on progression free survival per response type (CR, PR and NR). With more data becoming available, the model could be updated with treatment specific response and progression free survival estimates.

Finally, on modelling approaches in general, these days there are many guidelines and check lists for building a health economic model and for corresponding parameter and uncertainty estimation.[22, 25-31] Hence, the choice of the model approach (decision tree, Markov model or DES) is extensively discussed in the literature, now even more then when I started the thesis. Still, this doesn’t imply that each researcher will select the same modelling approach when considering the same chronic disease, as the choice of the modelling approach also depends on the question at hand and no “cookbook” exists. In this thesis, I have illustrated such absence of a “cookbook” and developed and motivated approaches targeted at the specific questions for the chronic diseases of schizophrenia, cardiovascular disease and multiple myeloma, with specific attention to reimbursement authorities’ requirements and preferences and methodological challenges in designing models for highly individualized treatments (schizophrenia), linked to trials with composite endpoints (cardiovascular) and for sequencing (multiple myeloma).

**Country adaptations**

Generally when conducting country adaptations of a core model for local reimbursement submissions, changing the discount rates, general population mortality rates, utilities, unit costs, and resource use to the new local setting is sufficient. However, when developing an applied model for local reimbursement purposes one should consider the possibility that in different countries other treatment settings apply. In that case the model adaptation might require structural model changes that ideally have already been anticipated when developing the core model. Often during the reimbursement process there is not sufficient time for implementing structural model changes.

My colleagues and I performed country adaptions for all models shown in this thesis, and made various subsequent publications.[1, 3, 5-10, 12] When developing the schizophrenia model, we encountered more structural challenges across different countries than for the other models considered. For instance, it became apparent that the link between having a relapse/psychosis and hospitalization or other types of resource use was not that well defined in the literature. Hence, when asking local experts about that link, the answer we got was, “well that depends”. The answers to “on what does it depend?” were heterogeneous across the countries. For instance, when developing the schizophrenia models in the UK, danger to oneself and/or society was the most important reason to go to hospital (which is an important cost driver), whereas in Germany danger was not considered at all as a reason for hospitalization.[6, 8, 21] These feedbacks obviously have impact on the model structure and different structures for the UK and Germany are obviously warranted. Also, the locations where patients are treated and the intensity of treatment in these locations differed substantially across countries.
So it is important when developing a model for non-fatal chronic diseases with serious events such as relapse in schizophrenia, to consider potential differences in how this disease and/or these events are treated across countries and address possible differences when building a core reimbursement model. In this thesis and with the schizophrenia model, I illustrated how a flexible methodology can be derived to achieve this. Notably, this can be exemplary for other situations, models and settings.

Model parameter estimation

Compliance

In case a new product is expected to have a relevant real-world difference in compliance compared to the comparator and it is expected to result in a comparative effectiveness difference with potential impact on health economic outcomes, compliance should be included in the health economic evaluation for reimbursement submissions. Notably, this is not only to show the full benefits of the new pharmaceutical, but also to be methodologically correct. There are however some issues, and the methodology is still in its infancy. Notably, it seems yet unclear how health authorities consider and value compliance in health economic evaluations and compliance data availability is often limited. Also, accurately incorporating compliance data in health economic models remains a challenge. The lack of good data to model compliance might explain the reluctance of health authorities to consider compliance benefits for health economic evaluations. Yet, from a methodological point of view, it is important to do so!

EMA phase III registration RCTs are designed to demonstrate efficacy and safety of the use of new products in controlled circumstances. Due to these controlled contexts, trials are not ideal for estimating compliance (differences) and its consequences in real world practice. Moreover, if compliance is measured in clinical trials, the measurements often seem unreliable and the trial compliance may not be reflective of real clinical practice. Hence, real world studies are needed for accurately measuring levels of compliance and the corresponding relative effectiveness. These data, however, will likely not be available for the new product when the reimbursement process is taking place, just after EMA marketing authorization. In that case one could consider the approach by Treur et al (inclusive myself as co-author, but not part of this thesis). In that study we assessed the health economic consequences of a compliance benefit resulting from a formulation that reduces the number of required pills per day. We used a pill intake prediction model, which was based on compliance from a real world database, to distinguish the probability that a patient would take its pill (on the right time) for both formulations over time. We linked those probabilities to pharmacokinetic and dynamic (pk/pd) dose response models to define a link between compliance and efficacy. As such we were able to show how the potential compliance benefit would translate in a health economic benefit using a patient simulation model. These real world compliance patterns linked to dose response models, which can be based on pk/pd studies or when
available on trial compliance data, could be a good start for accurately capturing the impact of compliance on effectiveness and therefore cost-effectiveness. Future research could entail developing treatment real world evidence (RWE) simulations. These combine the trial data of the new product with real world data on dose, diagnosis and adherence of existing products and with trial based dose response or compliance effect models, to predict real world effectiveness of the new product. These RWE effectiveness predictions could be included in health economic models, which would improve their predictions. These RWE simulations could help for instance demonstrate the value of a product with a compliance benefit, which is not captured in a clinical trial.

In the meantime, in countries that allow for it, manufacturers might consider offering a patient access scheme (PAS) \(^{[40, 41]}\) in which relative patient compliance data but more importantly its consequences on relative effectiveness are captured and subsequently implemented in the health economic model for reimbursement/pricing re-negotiations. In case a new product demonstrates a true relative compliance benefit resulting ultimately in a health economic benefit, the question remains, however, whether health authorities should award the new product a premium price. The answer is not straightforward from a health economic perspective. It might very well be that the old standard of care was reimbursed based on the efficacy results from a clinical trial without considering its real world compliance consequences (on health economic outcomes). Obviously and mentioned above, patients are often more compliant in clinical trials compared to clinical practice \(^{[38]}\). In that case it is possible that the current standard of care is under performing rather than that the new product is over performing. From a health-economic perspective, one could consider to give standard of care a price cut rather than giving the new drug a premium price.

The schizophrenia model presented in chapter 3 of this thesis was developed to assess the cost-effectiveness of long acting risperidone.\(^{[21]}\) The expectation modeled was that the long acting formulation would increase patients’ compliance in clinical practice and therefore reduce the number of psychotic episodes compared to oral atypicals, which were expected to be positively correlated with expensive hospitalizations. The trials for EMA registration purposes were non-inferiority trials and not designed to show an efficacy benefit due to the expected compliance benefit over oral risperidone. As such, the compliance estimates and the corresponding impact on effectiveness required for the model, had to be derived from literature and confirmed by expert opinion. At the time, no real world compliance databases existed for oral and long acting formulations. Ideally, for estimating the true impact of risperidone long acting’s compliance benefits for modelling purposes, we would have had real world data on the consequences of compliance and persistence differences in terms of effectiveness for both products. In several countries, the model was used to support the reimbursement submissions, arguing that a favorable cost-effectiveness ratio existed in high risk non-complaint patients, of long-acting risperidone.\(^{[1, 5, 7]}\) Since then, several real world studies have attempted to assess the effectiveness of long acting risperidone in clinical practice. A review by Kirsten et al concluded that long acting formulations
displayed significant advantages in nonrandomized observational studies, whereas in RCTs no difference was observed.\textsuperscript{[42]} There are only a few clinical practice studies comparing risperidone long acting with oral antipsychotics. These studies’ conclusions vary from no benefit of treating patients with long acting risperidone to a potential benefit.\textsuperscript{[43-45]} These studies applied different study designs, and all conclude that limitations in their study design might have impacted the results and all recommend further research. Compared to the long acting first generations antipsychotics, three studies found no additional benefit for long acting risperidone in clinical practice.\textsuperscript{[46-48]} The heterogeneity in study design and issues with respect to compliance in real world studies show the need for consistent use of standardized real world comparative effectiveness methodologies (with respect to compliance), as the design could affect the outcome.\textsuperscript{[49-53]} It also shows the value of flexible pricing systems based on real world evidence, such as considered in the UK.\textsuperscript{[41]}

My methodological contribution in this specific area of modelling compliance in cost-effectiveness models can currently be summarized as developing a health economic model in which the potential compliance benefits of long acting risperidone are implemented. Further work has resulted from this and should result from this, notably considering relative effectiveness demonstrated in rigid real world comparative effectiveness studies based on registries of high quality and validity. Such real-world evidence studies can often not be conducted prior to reimbursement. However, real-world evidence simulations can be conducted, considering both patient and clinician adherence. The results could be implemented in health-economic models. This could be a good start to improve health economic predictions in models considering diseases requiring chronic treatments.

**Sequencing**

Obviously, often local treatment guidelines recommend different subsequent treatments than those applied in the trial(s) and it is expected that the incremental cost and or effects differ due to the differences in subsequent and previous treatments. Ergo, adequately modelling clinically relevant sequences is crucial. At least two-treatment-lines-sequencing health economic models need to be developed in many cases. However, in indications with many treatment combinations that can be applied in numerous treatment lines (e.g. myeloma and rheumatoid arthritis), a two-lines-sequencing model might not be sufficient to accurately capture the full disease course and full impact of a treatment on the disease course. In that case sequencing models that consider more sequences might be needed. With such a model one would be able to address questions like: “what is the optimal treatment sequence?” and “what is the optimal place/line of individual products/combinations in these sequences in clinical practice?”. However, most EU health authorities face the question whether a specific new product for a specific treatment line brings value for money. Hence, the questions of the optimal sequence and optimal place of a product in a sequence are currently not relevant for reimbursement processes in most EU countries. Still, sequencing models are already relevant
for informing national or local formulary/treatment guidelines by clinicians and sickness funds and more relevance for national authorities can be envisaged. Moreover, sequencing could be relevant for health authorities that allow for outcomes-based PAS and subsequent pricing/reimbursement re-negotiations based on multi-technology appraisals such as NICE. In this system NICE can decide whether to recommend a product after EMA marketing approval based on pivotal trials and corresponding cost-effectiveness. Subsequently, it can further optimize the product’s treatment recommendation in this indication based on the outcomes of the PAS and subsequent results of the health economic sequencing model.

A limited number of health economic models aimed to assess the optimal treatment sequence in oncology have been published so far. An example of a sequencing model for multiple myeloma is presented in chapter 5. In myeloma, the introduction of thalidomide, bortezomib, and lenalidomide over the past 7-15 years have warranted a focus on the question of optimal sequencing of treatments. In first line treatment of stem cell transplantation (SCT) ineligible patients, thalidomide, bortezomib and lenalidomide are often combined with melphalan/prednisone or dexamethasone. In relapsed patients, these agents are typically combined with dexamethasone, but can also be administered as monotherapy. Hence, many treatment options, and therefore many treatment sequences, are available for clinicians and even more will become available due to introduction of new treatments. This warrants the question of the optimal sequence and therefore the need of a sequencing model. The first problem we encountered when developing the sequencing model was that treatment combinations that are often applied in clinical practice were not studied in RCTs, such as bortezomib in combination with dexamethasone, and thalidomide (combinations) both in relapsed patients. As the model was supposed to reflect clinical practice, we first tried to develop a model based on a regression in which aggregated RCT data were combined with aggregated data from real world evidence studies to ultimately estimate overall survival of the relevant sequences. When trying to get this published an important critique from journals was that one cannot pool RCT data with data from real world evidence studies. Therefore we decided to develop a model based on only the strongest level of evidence, i.e. RCT data. The disadvantage of that approach is that the model presented in chapter 5 cannot capture some of the sequences that are applied in clinical practice, due to lack of RCT data. Moreover, due to a lack of data on important inputs, some important treatment sequencing issues could not be addressed, such as cross-resistance between subsequent treatments, the influence of response on prior treatment to expected response on new treatment and impact of patient characteristics on response to treatments. These issues are under consideration for a forthcoming model update in which patient-level real world data will be incorporated. Ideally, these data would cover the effectiveness of all relevant sequences. An example of a sequencing model based on such a dataset (the FOCUS RCT) was presented by Manca et al for advanced colorectal cancer. No such a RCT dataset exists for multiple myeloma, due to the many treatment combinations, treatment lines and therefore sequences applied in clinical practice. There are however non randomized (retrospective) real world datasets
available for multiple myeloma that could be used to assess the impact of these issues in clinical practice. However, if the sequencing model should include new treatments and existing treatments, still assumptions are required for combining the RCT data from the new product with the real world data from the existing products before implementing the new treatment in the sequencing model. The number of assumptions required depends on the richness of the real world data set.

Future research is needed on linking efficacy phase III RCT data with real world effectiveness data. For instance for comparators that are applied in clinical practice, but for which no pivotal trials exists, as we encountered when developing the multiple myeloma model. In that case there is no common comparator but also the quality of the evidence is likely to differ substantially between trial data and real world data set. For this purpose the technique by Signorovitch et al. might be a good starting point to get relatively unbiased estimates of the relative treatment effects. The matching adjusted indirect comparison (MAIC) is not perfect in that respect as it only corrects for differences in patient characteristics and potentially treatment characteristics, but not for differences in quality or setting of the trial compared to real world studies.

Few health economic models have been developed that aim to compare effectiveness and cost-effectiveness of treatment sequences in oncology. My methodological contribution in this specific area of modelling can currently be summarized as developing a RCT based sequencing model for multiple myeloma. Further work has resulted from this which is currently ongoing. The challenge will be to combine data from observational studies with the RCT data to ensure the model captures all subtleties of sequencing such as cross resistance between treatments in different lines of a sequence.

**Multinomial end-points**

When conducting a PSA, it is important to consider correlations between end-points that serve as inputs in a health economic model, as these correlations can ultimately influence the point estimate and corresponding uncertainty of the ICER. This is demonstrated in chapter 6 where a method was introduced to include the correlations between MI, stroke and death for PSA purposes when considering individual trials and in a meta-analysis framework. This new method is compared with the standard Dirichlet approach that does not consider these correlations. Our findings show that the stronger the correlation between end-points, the stronger the reduction in uncertainty. In our paper, the correlation between these end-points was chosen arbitrarily. Further research could focus on deriving these correlations for the considered end-points. Whether the method presented is useful for reimbursement purposes depends mostly on whether uncertainty over the ICER is an important factor in reimbursement purposes, which is discussed in the next paragraph.
In case of ordered categorical outcomes, the selection of the statistical network meta-analysis (NMA) model should consider whether the data does not violate the proportional odds (PO) assumption, as statistical models that consider the PO assumption reduce the uncertainty over the NMA outcomes and therefore ultimately over the health economic model outcomes. This was demonstrated in the paper presented in chapter 7. Here we demonstrated that the PO NMA model reduced the uncertainty over the pooled estimates of trial outcomes compared to the multinomial logistic model. The application of the presented statistical PO NMA model is, however, limited to datasets that fulfil the proportional odds assumption.

The methods presented in chapter 6 and 7 both considered multinomial outcomes, either ordered, or correlated for physiological reasons. However, these multinomial methods can also be applied for NMAs concerning end-points that are mutually exclusive but not ordered or correlated. Ades et al conducted a multinomial NMA for the following end-points in schizophrenia; relapse, discontinuation because of intolerable side effects, and discontinuation for other reasons. In this regard, future updates of the schizophrenia model (chapter 3) should consider the multinomial network meta-analyses approach presented by Ades et al.

For the moment, I note that my contribution to the methodologies in this area can be summarized as developing a new methodology for considering correlations between (combined) multinomial end-points for PSA. This method could ultimately reduce the uncertainty over the outcomes of corresponding health economic models. Moreover, our paper on NMA methods for ordered categorical outcomes showed the importance for considering whether the underlying data does not violate the PO assumption. NMA methods considering the PO assumption could also ultimately reduce the uncertainty of the outcomes of corresponding health economic models.

Predictive factors for reimbursement decisions

My experience in modelling for reimbursement dossiers gave me the opportunity to have a methodological view on potential success factors for health economic models. We found that the submitted economic evidence in terms of the ICER and the corresponding uncertainty were strongly influential for the reimbursement recommendation by SMC. The other variables that showed a significant impact in the multivariate analyses, were related to the indication, whether the product was indicated for nonchronic use and whether the submission originated from a relatively large pharmaceutical company. In most EU countries, the impact of the ICERs and corresponding uncertainty on reimbursement decisions is unclear, as no local official ICER threshold has been published. The exception is England where NICE published an official ICER threshold. It is important to understand what the impact of the ICER and the corresponding uncertainty is on the reimbursement decisions. For that purpose a total of 463 appraisal documents (full submissions and resubmissions)
published on the SMC website between January 2006 and July 2013 were reviewed and extracted and analyzed by means of logistic regression.

Our findings imply that adequately implementing a full uncertainty analysis is not only a methodologically challenging academic exercise, it also matters for reimbursement decisions. So it is important to carefully select and consider techniques as presented in chapter 6 and 7 when building a health economic model, both from the point of view of innovative methodological approaches but also for successful reimbursement dossiers.

Other authors investigating other health care systems often had similar findings.[64-66] However, in the Netherlands the ICER seems not to be a strong predictor for reimbursement purposes.[67] Further research is suggested in chapter 8, e.g. similar analyses in other countries with consistent methodologies, inclusion of other soft factors in the analyses and multinomial regression rather than logistic regression for the outcomes of “recommended”, “recommended with restriction” and “not recommended”. Application of the methodology I developed in this thesis can thus further clarify differences and similarities in factors explaining reimbursement across Europe.

**Future of EU HTA collaborations for reimbursement purposes.**

Local health authorities face difficult reimbursement decisions. These decisions are especially difficult in case the clinical benefit of a drug has not been demonstrated in clinical trials, such as for instance was the case for long acting risperidone (chapter 2 and 3) or drugs that are approved by EMA based on a single arm trial (e.g. conditional marketing authorization).[68] The aim of this paragraph is to further elaborate on the (future) context of modelling chronic diseases for reimbursement purposes, specifically how PAS and health economic models could inform local reimbursement decision making.

Numerous countries allow for PAS.[40] There are two types of PAS: financially based and outcomes based. In the Netherlands and the UK several outcomes-based patient access schemes are and have been conducted. For reasons of efficiency, it seems that local health authorities, manufacturers and the EMA should collaborate on suggesting and designing post marketing studies for PAS that aim to inform local health economic models that are used locally to inform reimbursement/pricing renegotiations. Due to potential high costs of such registries, drugs to be analyzed should possibly be carefully selected. Eligible drugs for such a procedure would be drugs for which an added benefit is claimed and therefore a premium price is suggested by the manufacturer, but for which it is unsure whether the claim is true and really applies to clinical practice. Practically, this could imply drugs approved by EMA’s conditional marketing authorization, as the clinical information on relative efficacy is often limited for those and the manufacturers of these drugs have the obligation by EMA to conduct post marketing studies anyway.
From a health-economic perspective, there are a couple of conditions to make such an approach even more efficient. First, countries participating should define an ICER threshold and standardized health economic models, as otherwise it is difficult to define what a manufacturer needs to show in a PAS to either maintain, reduce or increase the price from a health-economic perspective. Moreover, the prospective evidence collected should be rigid and use standardized study designs \(^{49,50}\) and allow for comparative effectiveness analyses. All in all, major attention should be drawn in the coming years to make the information from real-world observational as informative for health economic modelling as possible.

**Future clinical development from health economic/reimbursement perspective**

The results of the health economic analyses seem to be important drivers for local reimbursement decisions, as was demonstrated for SMC in chapter 8, but also for other countries by other authors. \(^{64,66}\) A negative reimbursement decision is likely to have an impact on whether the drug is prescribed by clinicians. As the results of models are highly dependent on the underlying clinical trial evidence and many countries consider health economic evidence for reimbursement, it is important to already consider various health-economic requirements when developing phase III trials. To optimize clinical development for reimbursement purposes, one could consider the following approach: based on early clinical data (e.g. phase II results), conduct a phase III trial simulation \(^{69}\) before initiating the phase III trial. In case the design concerns surrogate end-points, consider whether there is sufficient evidence that converts the surrogate end-points to hard clinical end-points. Conduct an indirect treatment comparison \(^{70}\), as different countries may have a different standard of care. Next, an early health economic model should be developed that combines the trial simulation with the indirect treatment comparison, the data/method that extrapolates the trial data, the economic input data and quality of life data. Subsequently, conduct a value of information analysis on the model to determine which of the input parameters cause most of the uncertainty over the ICER.\(^{71}\) Based on these findings, adjust the trial simulation settings and re-run this procedure until the optimal trial design balancing reimbursement, registration requirements, and costs is found. Note that in the studies presented in this thesis, value of information analysis was generally not performed.

**Conclusion**

From the SMC reimbursement database analyses (chapter 8) it was learned that, among other points, for a drug indicated for chronic use the ICER and the uncertainty surrounding the ICER are significant factors for a successful reimbursement submission in Scotland. So when building a health economic model it is important to adequately consider uncertainty analysis, next to the general pros and cons of the various modelling approaches (e.g. in terms
of data requirements, medico-scientific experience, simulation time, clinical representation, their ability to deal with patient heterogeneity, the timing of events, the relevance of prior events, patient interaction, interaction between covariates and variability), and whether the same model structure can be applied to all countries. In case the model considers competing clinical risks as inputs, it is important to consider correlation between those risks. Otherwise, one might overestimate the uncertainty around the model results, which may impact the reimbursement decision. Crucial topics addressed in the thesis additionally refer to adequate inclusion in the model (if appropriate) of compliance and treatment sequencing.

To conclude, some crucial issues to consider in health-economic modelling for reimbursement of drugs in chronic diseases are addressed in this thesis. These comprise the complexity of the model, the precise alignment of clinical trial information and the health-economic model in terms of populations covered, line of treatment and corresponding exact claims of the manufacturer, use of composite versus surrogate endpoints and methodological issues concerning multinomial data and dependency of clinical events. It is of utmost importance that the manufacturer, the researcher, and the authorities are on par on these issues to achieve adequate reimbursement decisions for innovative drugs that improve the health of populations. Adequate and transparent models using innovative methodologies can help in this respect and were suggested and developed within this thesis. This requires expertise and open communication from all three sides mentioned, with the ultimate goal to enhance healthy aging of populations.
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