1. Introduction
Drug development is a long and expensive process with a high failure rate\textsuperscript{[3]} Recently, DiMasi et al. reported a clinical approval success rate of 19% for drugs that reached the phase of human clinical research to regulatory approval.\textsuperscript{[2]} Most drugs don’t even enter the phase of human clinical research. The entire process from drug discovery to finalizing the clinical program takes around 10 to 15 years. The reported cost to bring a new chemical entity to market ranges from $55 million to $2 billion.\textsuperscript{[3-6]} The aim of the manufacturer is obviously that these investments are offset by use in clinical practice, for which a positive reimbursement decision is crucial. Absence of reimbursement generally means absence of use. Nowadays, in most European countries favorable health-economic evidence based on sound health economic models is required for positive reimbursement decisions.

This thesis focusses on the use of chronic disease health-economic models for reimbursement decisions. Both theoretical issues and illustrative examples in mental and somatic chronic diseases will be provided. The paragraphs below describe the process from drug development to European local reimbursement. Subsequently, it introduces the challenges and corresponding questions for when developing a chronic disease health economic model in terms of choosing the right modelling approach, country adaptations, model parameter estimation and whether model results impact reimbursement decisions. The peculiarities of such modelling for reimbursement authorities while keeping to high scientific standards or even developing new methodologies will be highlighted in this thesis.

**Drug development**

Prior to being allowed to be prescribed and used in clinical practice, a drug is tested over an extensive period in the laboratory, in animals and finally in humans; i.e., the pre-registration or pre-marketing phase of drug development. The pre-marketing phase can be divided in pre-clinical and clinical stages. The pre-clinical phase includes discovery, synthesis and animal testing of the drug. During the clinical phase the drug is tested in clinical trials in humans. The human clinical trials are generally divided in three phases. In phase I trials a new drug or treatment is tested in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.\textsuperscript{[7]} In Phase II trials new drug or treatment is tested in a larger group of people to see if it is effective and to further evaluate its safety.\textsuperscript{[7]} Phase I and II trials can overlap, as for instance there are some obvious limitations in testing oncology drugs in healthy volunteers. Many drugs fail in phase I and II trials, after which clinical development is mostly stopped.\textsuperscript{[1, 2]} Phase III randomized controlled trials (RCT) are the most rigorous and expensive trials. In these trials the new agent is compared with either placebo or an active comparator. Usually, both patients and clinicians participating in the trial are blinded (i.e. they don’t know whether the new drug or the comparator is provided). In phase III trials the drug or treatment is given to large groups of people to confirm its efficacy, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used a safe and efficacious as possible.\textsuperscript{[7]} Generally in
Europe, based on phase III RCTs, manufacturers can file for local or EU Marketing approval by the European Medicines Agency (EMA).

After marketing approval, manufacturers may conduct phase IV trials. Phase IV studies are done when the drug or treatment is already marketed to gather information on the drug’s effect in various populations and any potential side effects associated with long-term use. Research in phase IV can be voluntary at the initiative of the manufacturer to gather real-life insights. It may also be obligatory by local health authorities to gather real-life evidence, for example, under patient access schemes (PAS), pharmacovigilance investigations and conditional reimbursement.

Local and EU marketing approval

The EMA is responsible for the scientific evaluation for EU market access approval of medicines developed by pharmaceutical/biotechnology companies for use in the European Union. This European centralized procedure is mandatory for certain medicines, e.g. orphan drugs, medicines derived from biotechnology, and medicines for certain indications, e.g. cancer, HIV infection and diabetes. For medicines that do not fall within these categories, companies have the option of submitting an application for a centralized marketing authorization to EMA. Alternatively, companies can file for registration in the individual countries. Both the EMA and the local marketing approval authorities evaluate whether a drug is safe and effective for use, predominantly based on phase III trial results. However, with EMA’s conditional marketing authorization procedure for medicinal products for seriously debilitating or life-threatening diseases, emergency threats and orphan diseases, also products enter the market based on single arm phase II or III trials. Up to this stage, health economics and therefore health economic modelling plays no role in the approval decision.

Reimbursement in individual EU countries

After EMA marketing approval, the drug can be sold in Europe. However, in most countries drugs are not automatically reimbursed after marketing approval (besides, for instance, in Germany and England; where of course specific mechanisms such as price negotiations do apply). Without reimbursement the market uptake of the drug will generally be limited. Hence, getting reimbursement for new drugs is crucial for pharmaceutical companies. The EMA and local marketing approval agencies are not authorized for making the decision on whether a drug is reimbursed in the individual European countries. Local health authorities are granted that responsibility. However, throughout Europe the decisions to reimburse new individual pharmaceuticals are under pressure, due to increasing pharmaceutical costs and health care costs. One of the factors involved here is that in most European countries populations are aging and therefore numbers of inhabitants with chronic diseases are increasing. Local health authorities currently face tough decisions regarding how to keep
care affordable, inclusive potentially not reimbursing all new health-care technologies that become available. Hence, the choice of whether to reimburse individual new pharmaceuticals has become a difficult one, and will likely not become easier in the future. One criteria for reimbursement is often related to the health-economic profile of a drug. Clearly, health-economic considerations play an increasingly important role in reimbursement decisions.

Local European health authorities make these reimbursement decisions by evaluating the available clinical and economic information. The required clinical and economic evidence that manufacturers need to submit and the weight of the individual pieces of evidence that play a role in the reimbursement decision differ substantially across European countries. For instance, Germany introduced a new reimbursement system for pharmaceuticals in 2011.[16, 17] In the German system, drugs that have received EU or local German marketing approval will be reimbursed at a relatively free price level for one year after launch. During that year the manufacturer is required to submit the relevant clinical and economic evidence in a standardized reimbursement dossier to the “Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG)”, that will subsequently provide a recommendation based on that evidence to the “Gemeinsame Bundes Ausschuss (GBA)” on the assessed added value of the drug. GBA will make a final decision on whether or not the drug seems to provide adequate added value based on the currently available evidence. Based on the added benefit decision the “GKV Spitzenverband” (organization representing the German sickness funds) will start price negotiations with the pharmaceutical company. This price will apply after the one year since market entry. Notably, in Germany, the economic evidence required to support this process that occurs within first year of market entry, primarily concerns budget impact; no formal health economic evaluation is required.

Similarly to Germany, in England, after a new drug is registered by the EMA, the drug does not automatically need to go through a formal reimbursement process. The prices of branded prescription medicines supplied to the National Health Services (NHS) are currently controlled by the Pharmaceutical Price Regulation Scheme (PPRS). This is a voluntary agreement between the Department of Health (DH) and the pharmaceutical industry.[18] Manufacturers can additionally offer a patient access scheme (PAS), either financially or outcome based.[8] PASs are proposed to improve the health technologies’ cost-effectiveness. The advantage of a PAS over direct price cuts for manufacturers is that it is not reflected in the English list price and therefore doesn’t affect prices in other countries. The National Institute for Health and Clinical Excellence (NICE) evaluates the clinical benefit and cost effectiveness of health technologies for the NHS. Contrarily to the German setting, NICE does not negotiate drug prices, but after launch NICE can decide to appraise a new drug in a single technology appraisal (STA) process.[19] In 2008 around 40% of drugs new to the UK market were evaluated by NICE.[18] For drugs that do not undergo an STA at market entry, NICE still can, at a later stage, decide to assess the product in either an STA or a multiple technology appraisal (MTA).[20] In case of the latter, NICE considers all drugs in the indication simultaneously, rather
than focusing on an individual drug - as is done in an STA. The evidence pieces that the pharmaceutical companies are required to submit to NICE for an appraisal process concern an assessment of the burden of illness, an overview and critical review of the clinical evidence of competitors and of the new drug itself, and of the previously published economic evidence. This information is combined with the manufacturer’s health economic case on the balance between (long term) costs and health effects in the standardized appraisal report of NICE. Thus, in England the required economic evidence is much more elaborate than a simple budget impact analysis as in the German context.

Contrarily to Germany and England, in most other European countries (e.g. the Netherlands, Sweden, Spain, Italy, Poland, Portugal and Scotland), the drug first needs to undergo a formal reimbursement application before it is considered for reimbursement. The main components of these reimbursement dossiers include both the available clinical and health economic evidence. Only a positive opinion on all these components leads to a decision to reimburse by the local governments.

Regarding the final HTA recommendation and consequences, in Germany the final price of the new pharmaceutical depends mostly on the added clinical benefit and the budget impact of the new agent.[16, 17] In England, the final NICE recommendation heavily depends on the health economic outcomes, i.e. balance of costs and effects (cost-effectiveness). In fact, NICE is the only health authority that publishes explicit thresholds below which a drug is considered cost-effective and therefore eligible for recommendation.[22] In most other EU countries mentioned above, the cost-effectiveness of a drug plays a role in the reimbursement decision, but its relative weight in the decision of whether to reimburse is often unclear. In these countries, pharmacoeconomic guidelines and practices do not explicitly mention when a technology is considered cost-effective and therefore whether it should be reimbursed or not.[23-25]

### Health economics

The local health technology assessment (HTA) agencies, e.g. AOTM in Poland¹, TLV in Sweden², Zorginstituut Nederland³, IQWIG in Germany⁴, NICE in England⁵ and Scottish Medicines Consortium (SMC)⁶, face a difficult task in evaluating whether a new drug represents value for money and thus, whether the drug should be reimbursed. The application of health economics reflects a universal desire to obtain maximum value for money by ensuring not just

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the clinical effectiveness, but also the cost-effectiveness of healthcare provisions.\textsuperscript{[24]} A cost-effectiveness analysis (CEA) is a form of economic analysis that compares the relative costs and outcomes (effects) of two or more courses of action (e.g. two or more pharmaceuticals) over time. The time horizon considered in a cost-effectiveness analysis is generally the duration the treatment is expected to affect the patient’s disease in terms of quality of life and and/or costs.\textsuperscript{[24, 27]} For chronic diseases this often implies a life time time-horizon. The following cost types can be distinguished in a health economic evaluation: pharmaceutical costs, direct medical costs, indirect non-medical costs (e.g. productivity losses), direct non-medical costs (e.g. travel costs) and indirect medical costs (e.g. in cases of curative interventions patients may get other diseases in life-years gained which are attributed with resource use and therefore costs).\textsuperscript{[24, 27]} Regarding effectiveness, any health related outcome can be included, but most cost-effectiveness analyses have Quality Adjusted Life Years (QALY) as the main outcome. With utility as the main concept underlying the QALY, cost-effectiveness analysis is also referred to as cost-utility analysis if the QALY is considered.\textsuperscript{[27]} The QALY is definitely the recommended effectiveness measure in most health economic guidelines.\textsuperscript{[11, 20, 24, 25]} The advantage of the QALY is that it is an outcome that can be applied to all diseases and therefore it allows analyses to seek the most efficient distribution of limited health care resources over multiple diseases.

The primary outcome of a cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER).\textsuperscript{[27]} The ICER and the corresponding uncertainty around this outcome are used for supporting reimbursement decisions. By using generic outcomes such as costs and QALYs, one can define and apply cost-effectiveness thresholds below which a drug can be considered cost-effective. As said, in Europe, the only country with an explicitly published threshold is England. NICE considers drugs with an ICER below £20,000-£30,000 per QALY as being cost-effective and therefore eligible for recommendation in their clinical recommendations.\textsuperscript{[22]} Nevertheless, NICE suggests that various other factors should also be taken into account and exceptions are made, for example, concerning end-of-life drugs and orphan drugs on the basis of additional criteria such as equity and disease severity. For other European countries such as the Netherlands\textsuperscript{[28]} implicit thresholds have been published but they are not formally recognized by the respective health authorities.

**Modelling**

A mathematical model is a description of a system using mathematical concepts and language.\textsuperscript{[29]} A model may help to explain a system, study the effects of different components, and make predictions about behavior. In health economics, cost-effectiveness analyses are formalized in health economic models that combine clinical (often from phase III trials), epidemiological, economical and quality of life data. The main aim of these models is to assess whether a drug or other healthcare technology is cost-effective. There are several types of models that can be applied. For instance, one can collect the relevant data in a
phase III RCT to conduct a within-trial cost-effectiveness analysis, which is formalized in a statistical framework. For chronic diseases though, trials mostly do not consider all relevant information or the duration of the trial is not long enough to capture the full implications of the new drug for a within trial cost-effectiveness analysis. The latter is often the case for chronic diseases. In those cases more elaborate health economic models can be developed. Here, the outcomes from the clinical trial(s) are linked with epidemiological data and/or econometric techniques are used to extrapolate the disease over time. For this purpose, health states are often defined that describe the disease progression over time. Subsequently, the health states are linked to relevant utility and cost estimates. The time spent in each of the health states multiplied with the corresponding utilities result in the patient’s QALY.

Regarding the model structure and frameworks, several options exist that could be applied when building a model for a chronic disease. The simplest type of model is a decision tree, which uses branches to describe the decision problem. Costs and effects are linked to the branches (health states) and the probabilities to enter a branch often depend on clinical trial data and potentially the epidemiological data used for the extrapolation of the trial results. The second type of model that can be applied is a Markov model. Markov models assume that a patient is always in one of a finite number of discrete health states, the “Markov states”. All events are represented as transitions from one state to another. Notably, Markov models generally lack history (i.e. they are ‘memory less’). If this characteristic of the Markov model becomes problematic, adaptations (i.e. including “tunnel states”) or alternative types of modelling should be considered. The third type of model is a discrete-event simulation (DES), in which the disease is represented as a chronological sequence of events (health states). Each event occurs at an instant in time and marks a change of the state of the disease. This type of model simulates the time between events of individual patients over time.

**Challenges to model development and corresponding questions**

Health-economic requirements concern most new drugs, but are most imminent for chronic diseases as these require long-term drug use with corresponding long-term costs. Hence, when developing a chronic disease health economic model for reimbursement purposes, one needs to consider among others the following four topics, modelling approach, country adaptations, parameter estimation and impact of modelling results on reimbursement authorities. These four topics are addressed in this thesis by nine formulated questions, which are introduced below per topic.

Different health economic modelling approaches exist. Hence, the first question that needs to be addressed is which approach (decision tree, Markov model and DES) to select, which captures the relevant disease characteristics, which is adequately flexible, but still a generic model allowing application in various (European) countries. This question is addressed in chapter two, and chapters three, four and five present practical examples of three chronic diseases.
disease models, e.g. schizophrenia, cardiovascular disease and multiple myeloma. During the development of this thesis, also other researchers have addressed the question of selecting optimal modelling approach, leading to international guidelines and checklist for model development. [27, 32-39]

When developing a core health economic model that should be adjusted to different countries, the differences in health economic requirements and in treatment setting should be adequately addressed. Regarding the latter, RCTs for treatments of chronic diseases often have a limited duration. Hence, when building a model the trial data needs to be extrapolated to ensure the model captures a sufficient time horizon to demonstrate all relevant costs and effects of the new pharmaceutical over time. This is often complicated as not all countries have sufficient data for these extrapolations, but also the treatment setting may be different among the countries that are in the model. A standard country adaptation involves among others changing discount rates, general mortality estimates, resource use and unit costs and potentially utility estimates. The second question addressed in this thesis is whether differences across countries regarding treatment setting should affect the model adaptation?

With respect to model parameter estimation, the main sources/aspects for differentiating the considered treatments in a health economic model are often data the phase III RCTs and price. These trials are, however, designed to demonstrate efficacy and safety, in a controlled setting in selected patients, for the marketing approval decision by EMA. Contrarily, health authorities are most interested in how the drug performs in clinical practice rather than in the controlled environment of a clinical trial. Hence, the model needs to translate the efficacy measured in the clinical trial to effectiveness, i.e. how the drug behaves in clinical practice. Factors that might differ between clinical practice and clinical trials are compliance of patients and clinicians[40], (concomitant) drug use, and characteristics of treated populations. Please note that medication compliance and medication persistence are two different things. Medication compliance refers to the degree or extent of conformity to the recommendations on day-to-day treatment by the provider with respect to the timing, dosage, and frequency. [41] Medication persistence refers to the act of continuing the treatment for the prescribed duration. [41] Medication compliance is more problematic in chronic disease than in acute diseases. [40] Regarding compliance, due to the design of randomized controlled trials, it is difficult to show the full potential of long acting formulations. Patients are generally far more compliant in clinical trials than in clinical practice. [42] Hence, when comparing a long acting formulation (e.g. an injection administered every month) with the corresponding short acting formulation (e.g. oral administration every day), it is very likely that the phase III trial will show equal efficacy, whereas in clinical practice a long acting formulation might have huge advantages in term of effectiveness. So the third question addressed in this thesis is whether compliance benefits translated in health economic benefits should be considered for reimbursement purposes? Subsequently, the fourth question addressed is; what are the main issues when implementing compliance in a health economic model for reimbursement purposes? Both questions are addressed in chapter two and three.
With respect to sequencing, the EMA faces the question whether a specific new treatment is efficacious and safe in a specific treatment line/patient population? Correspondingly, phase III RCTs are generally designed to demonstrate that. Similarly to EMA, local health authorities face the question whether that treatment brings value for money in that population/treatment line? However, in clinical practice the treatment of chronic diseases such as rheumatoid arthritis and multiple myeloma often consists of a sequence of several lines of treatment that all affect costs and effects. So the fifth question addressed in this this is whether sequencing should be considered in models for reimbursement purposes? The subsequent sixth question is then; what are the issues are when developing a health economic sequencing model for chronic diseases? Both questions are addressed in chapter 5 of this thesis.

Also regarding model parameter estimation, the increasing demand for evidence-based medicine has been accompanied by an increasing need for trials to show effects of active treatment versus the comparator on “hard” (death, stroke or MI) endpoints rather than “intermediate” (e.g. progression free survival) or “surrogate” (e.g. cholesterol) endpoints. To reduce the number of patients needed in the trial and the duration of follow up, these trials are often powered on a significant difference in a combined endpoint (e.g. death, MI and stroke), accepting that the difference in the individual components may not be significant or that the result may even show a “wrong” direction for one (or more) of the individual components. When building a cost-effectiveness model on such trial evidence, the individual end-points are necessarily used for input, and not the ‘significant’ combined end-point, as costs, life expectancy and QALYs differ for the individual components in the composite endpoint. Hence, the uncertainty in the individual end-points will translate into the uncertainty of the model outcomes (i.e. the cost-effectiveness). Whilst the combined end-point is sufficient for EMA, local reimbursement authorities might critique the model outcomes as not being robust, due to uncertainty over the inputs. This may have consequences for local reimbursement decisions and it is crucial to fully understand the uncertainty introduced with this approach. The seventh question addressed in chapter 6 concerns; what is the impact of considering correlations between combined multinomial clinical end-points like MI, stroke and death on the outcome of health economic models?

Finally with respect to model parameter estimation, clinical studies often report patient outcomes on a categorical scale. For example cancer patients may be reported as having “no response”, “partial response” or “complete response” to treatment; a potentially very valid and relevant classification for registration authorities. The relative treatment effect on these ordered categorical scales may be the main differentiator between treatments in a health economic model. The relative treatment effects of ordered categorical data can be estimated with different statistical methods that have different underlying statistical assumptions and properties. These different assumptions and properties have consequences on fit, interpretability of relative treatment effects and amount of uncertainty in model parameters. Subsequently, when implemented in a health economic model these different statistical
methods can affect the ICER of the health economic model and the corresponding uncertainty. Hence, the eight question addressed in chapter 7 of this theses concerns; what is the impact of different statistical techniques for meta-analyses of ordinal categorical outcomes on point estimate and uncertainty over the resulting relative efficacy estimates? (chapter 7)

The impact of different ICERS and corresponding uncertainty on reimbursement decisions is unclear in most countries as no formal ICER threshold have been published, except for England. Hence the final and ninth question addressed in this thesis is, how important are the modelled ICER and corresponding uncertainty in the reimbursement decision of the Scottish medicines agency?

**Objective of the thesis**

Summarizing the above, on the one hand pharmaceutical companies face long and costly drug development programs with a high failure rate. On the other hand, local health authorities face an aging population resulting in a substantial increase in the prevalence of chronic diseases, which require chronic (pharmaceutical) treatment, resulting in an increasing pressure on health care budgets and therefore drug reimbursement decisions. As one consequence, more and more local European health authorities oblige pharmaceutical companies to submit valid and transparent evidence concerning the cost-effectiveness of their new pharmaceutical. These cost-effectiveness analyses are mostly based on a health economic model.

The aim of the present thesis is to assess the abovementioned challenges when developing health economic models for chronic diseases for reimbursement purposes in Europe. The focus will be on the following topics and questions directly resulting from these topics:

### 1. Modelling approaches

- Question 1: Is there an optimal modelling approach e.g. decision tree, Markov model or DES, for modelling chronic diseases for reimbursement purposes? (chapter 2-5)
  - What is the optimal modelling approach for schizophrenia for reimbursement purposes? (chapter 3)
  - What is the optimal modelling approach for cardiovascular disease for reimbursement purposes? (chapter 4)
  - What is the optimal modelling approach for multiple myeloma for reimbursement purposes? (chapter 5)

### 2. EU country adaptations

- Question 2: A standard country adaptation involves among others changing discount rates, general mortality estimates, resource use and unit costs and potentially utility estimates. The second
question addressed in this thesis is whether differences across countries regarding treatment setting should affect the model adaptation?

3. Model parameter estimation
   o Compliance
     § Question 3: Should compliance benefits translated in health economic benefits be considered reimbursement purposes? (chapter 2 and 3)
     § Question 4: What are the issues when developing a health economic model that considers compliance benefits? (chapter 2 and 3)
   o A trial focusses on one treatment line. In clinical practice however patients are treated potentially with many treatment lines/sequences.
     § Question 5: Should sequencing be considered in models for reimbursement purposes? (chapter 5)
     § Question 6: What are the issues when developing a health economic sequencing model? (chapter 5)
   o Multinomial end-points
     § Question 7: What is the impact of considering correlations between combined multinomial clinical end-points like MI, stroke and death on the outcome of health economic models? (chapter 6)
     § Question 8: What is the impact of different statistical techniques for meta-analyses of ordinal categorical outcomes on point estimate and uncertainty over the resulting relative efficacy estimates? (chapter 7)

4. Predictive factors for reimbursement decisions
   o Question 9: How important or the modelled ICER and corresponding uncertainty in the SMC reimbursement decision? (chapter 8)

Structure of the thesis
The thesis is presented in two parts. The first part focusses on modelling of chronic diseases. Here, modelling approaches of the three aforementioned chronic diseases are presented, i.e. schizophrenia, cardiovascular disease and multiple myeloma. The second part is about methodological issues related to developing models for chronic diseases for reimbursement purposes. These subsequent chapters describe issues concerning the uncertainty with analyzing multinomial trial outcomes that for health economic models and the consequences for the uncertainty over the model outcomes. This is followed by a chapter on assessing the impact on (health economic model) outcomes on the reimbursement decisions in Scotland.
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