

Managing the Introduction of High-Cost Medicine

A comparative analysis of the role of Managed Entry Agreements in Norway, the Netherlands, and England

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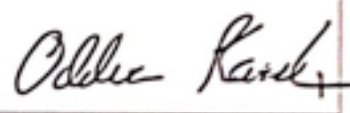
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Abstract

Background: Timely access to medicines is a significant objective of current health care systems. Nevertheless, concerns regarding the costs and effectiveness of medicines might slow down the process of introducing medicines to a market. Managed Entry Agreements (MEAs) are instruments utilised in many European countries to address concerns regarding the uncertainties in cost-effectiveness, budget impact, and real-life use. Within Norway, this concept has not been studied yet.

Objective: The aim of this study is to explore MEA utilization in a European context, and to further assess what lessons Norway could learn from European experiences.

Method: The conducted study included a country comparison across the Netherlands, England, and Norway. Further, semi-structured interviews were conducted in order to assess the current opinion about MEAs among Norwegian stakeholders.

Results: MEAs are applied across all three countries to target uncertainties in the introduction of high cost medicines. Overall, the application of financial arrangements is evident across countries. The main disease area targeted consists of antineoplastic and immunomodulating agents. Among Norwegian stakeholders MEAs are regarded as helpful instruments to improve timely access, however, stakeholders have been careful implementing these agreements due to the lack of good practices.

Discussion: MEAs consist of a range of policy instruments used in European countries. Although all countries applied MEAs, there is a differentiation in policies to describe them, the number, and type of applied agreements. Willingness to pay partly explains such variations. However, further scopes for research remain as confidentiality limit the cross-country comparison, and study of impact. This is the first study to include Norway in its comparison regarding MEAs.

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List of Abbreviations

Abbreviations used throughout the study:

ATC-code	= Anatomical Therapeutic Chemical Code
CED	= Coverage with Evidence Development
EMA	= European Medicine Agency
EU	= European Union
GVS	= Geneesmiddelen Vergoedingsstelsel: Medicine Reimbursement List
HELFO	= Helseøkonomiforvaltningen: Norwegian Health Economics Administration
HOD	= Helse- og Omsorgsdepartementet: Ministry of Health and Care Services
HTA	= Health Technology Assessment
ICER	= Incremental Cost-Effectiveness Ratio
LIS	= Legemiddelinnkjøpsamarbeid
MEA	= Managed Entry Agreement
NHS	= National Health Services
NICE	= National Institute for Health and Clinical Excellence
NOACs	= New Oral Anticoagulants
NoMA	= Norwegian Medicine Agency
OIR	= Only In Research
PAS	= Patient Access Scheme
PBRSA	= Performance-Based Risk-Sharing Agreement
PPRI	= The WHO Collaborating Centre of Pharmaceutical Pricing and Reimbursement Policies
PPRS	= Pharmaceutical Price Regulation Scheme
PSB	= Payer Strategy Burden
PUB	= Payer Strategy Burden
QALY	= Quality-Adjusted Life Year
RWR	= Recommended With Research
RHA	= Regional Health Authority
STA	= Single Technology Assessment
VOI	= Value Of Information
WTP	= Willingness To Pay
ZIN	= Zorginstituut Nederland: Dutch Health Care Institute

Chapter 1. Introduction

1.1. Background

Timely access to potentially beneficial drugs is recognised to be a significant objective within current health care systems. (Baird et al., 2014). Rapid introduction of these drugs to patients may offer them a significant perspective (Gerken et al., 2017). To optimize accessibility and affordability to valuable drugs, processes of marketing licensing, strategic pricing, and reimbursement are in place (Pauwels, Huys, Vogler, Casteels, & Simoens, 2017). Nevertheless, ensuring rapid access to potential beneficial drugs brings certain challenges to the accessibility and affordability within the current economic landscape.

The high cost of drugs are perceived as a main challenge in providing access to new treatments given budgetary constraints among European policy makers (OECD, 2015). The need to manage pharmaceutical expenditures results from an increasing demand for pharmaceutical products and new opportunities for treatment. Different causes contribute to the increasing demand including an ageing population, high expectations of patients about new treatments methods, a rising prevalence of chronic diseases, and the development of new promising drugs (OECD, 2015).

Moreover, the launch of new innovative treatments has always been surrounded with considerable uncertainty surrounding clinical and economic performance in the real-world (Garrison et al., 2013). Nevertheless, the risk related to new treatments not working out as anticipated has increased (Garrison et al., 2013). This challenge relates to the challenge of the high prices of new medicines not always being justified by high clinical benefits (OECD, 2015). The need to tighten health care budgets, result increasingly in the implementation of stricter processes in order to prioritize treatments that deliver demonstrable improvements in the quality of life, and efficiency targets (Klemp, Frønsdal, & Facey, 2011).

In addition, the European Medicine Agency (EMA) has taken upon a new approach into their efforts to ensure timely access, called 'adaptive pathways for medicine' (EMA, 2017). This change in the regulation of marketing authorization by the EMA, will result in the licensing of medicines at an earlier stage of evidence development (Grimm, Strong, Brennan, & Wailoo, 2016). As a result, assessments to decide whether drugs are eligible for reimbursement have to be carried out with less evidence. As health technology assessment (HTA) becomes more important in decisions, the lack in real-life data, especially for chronic disease, available at the time of market introduction becomes more problematic (Bouvy & Vogler, 2013).

Concerns about the cost of new therapies, and further lack of information on the effectiveness of therapies have increased the uncertainty related to the introduction of new treatments (Kanavos, Ferrario, Tafuri, & Siviero, 2017). The uncertainties related to clinical and economic performance, cause payers expressing the desire to obtain greater certainty and value for their investments (Garrison et al., 2013). As a result, uncertainty about financial and clinical performance may delay reimbursement decisions and patient access. The insufficient base of effectiveness data at the launch of a product, asks for additional reimbursement options, in addition to the existing paradigms for pricing and reimbursement.

In order to ensure rapid access, innovative instruments of pricing and reimbursement have been developed. *Managed Entry Agreements (MEAs)*, are one possible method to manage costs and uncertainties. An MEA is a formal agreement between a pharmaceutical manufacturer and a payer party, in order to enable access (coverage or reimbursement) to a health treatment subject to a specific condition (Grimm et al., 2016). MEAs overarch a broad, heterogeneous group of instruments, which can be utilised to address uncertainty regarding effectiveness of technologies, limit the impact of budget, or manage the use of technologies in order to optimize effective use (Grimm et al., 2016). Examples of MEAs include amongst others negotiated discounts, conditional reimbursement with evidence development (CED) schemes, or performance-based agreements.

Across a survey conducted among several European countries, Norway was one of three countries (besides Denmark and Finland), where MEAs are currently not implemented (Ferrario & Kanavos, 2013). Currently, stakeholders are not engaging in MEAs in Norway, although there has been limited experience with MEAs in the past (Ferrario & Kanavos, 2013; Grepstad Lundeby, 2014). Despite MEAs not being in place, there is a scope to share experiences between different European countries, since all countries have to look increasingly for innovative reimbursement options (Ferrario & Kanavos, 2015). Moreover, a need for new instruments becomes increasingly urgent due to the affordability, and issues related to opportunity costs (Vogler et al., 2016).

Application of MEAs across Europe continues to grow as pharmaceutical manufacturers and payer parties gain more insight into the utilization of MEAs, the related risks, and rewards (Carlson, Gries, Yeung, Sullivan, & Garrison, 2014). Nevertheless, despite numerous opportunities and advantages MEAs can deliver, there is significant scepticism across decision-making bodies towards MEAs (Kanavos et al., 2017). As a result, more knowledge is required on MEAs, their value, and its appropriate implementation to increase support for MEA implementation and its value in the Norwegian market. Therefore, this thesis aims to

explore MEA utilization in a European context, and to further assess what lessons Norway could learn from European experiences.

1.2. Research Questions

Within the context of the European Master in Health Economics and Management, a country comparison is included. Included countries are Norway, the Netherlands and England (including Wales). In order to structure the analysis of the aforementioned research aim the following sub-questions were conducted:

- In what way are arrangements, related to uncertainty, conducted for the introduction of new pharmaceutical product organized in different countries?
- What are different rationales for the use of MEAs?
- What causes the variation in MEA and non-MEA use, such as Norway, between different countries?
- How do Norwegian stakeholders value MEAs?
- What are the lessons Norway could learn from international experiences?

1.3. Thesis Structure

The thesis is constructed in six chapters including the introduction. The other chapters are chronological as the following: the theoretical framework, the research methods, the results including an analysis of the country comparisons, and an analysis of the stakeholder interviews, and the discussion and conclusion.

Chapter 2. Theoretical framework

The theoretical framework presents a discussion of prior theories and frameworks related to MEAs, in order to explain how MEAs could contribute to the introduction of high-cost medicine. Lastly, the chapter will close with a short review of the existing literature on cross-country analysis and experiences in Europe.

2.1. The Introduction of High Cost Medicine

Before introducing a new drug to the market, the drug has to be registered and approved for reimbursement. Reimbursement of pharmaceutical products in the current economic landscape ought to provide incentives for and reward the process of innovation. The set price should reflect the value of a product. The term value in the context of health care products usually integrates measures of health-related quality of life and costs (Mullins, Montgomery, & Tunis, 2010). The pathway of introducing a drug into a market involves the collaboration of multiple stakeholders. Market access and its timing is largely controlled by three parties including pharmaceutical and biotechnology companies, regulators, and HTA bodies and/or payers (Baird et al., 2014).

Pharmaceutical manufacturers are responsible for developing innovative medicines (Baird et al., 2014). They invest in markets as a result of financial attractiveness of developing large scale reimbursement in addition to the benefits of a granted temporary monopoly (de Pouvourville, 2006). Establishing a price, pharmaceutical companies need to bear in mind the minimum price necessary to keep the company financially sustainable, while on the other side it has to be kept in mind what buyers are willing to pay for a drug. Willingness to pay (WTP) is influenced by numerous factors including reimbursement systems, risk aversion, funding systems, and the price of competing funds in individual countries.

Payer parties function as the final gatekeepers of market access (Baird et al., 2014). Payer parties as well as HTA bodies are heavily involved in the regulation of pharmaceuticals within Europe. Pharmaceutical policies are imbedded in national frameworks at different levels of legal requirement, and different national policy objectives such as ensuring financial sustainability, equity, quality of care or while rewarding health innovation (Bouvy & Vogler, 2013; Leopold, 2014). To be eligible for reimbursement, there needs to be an assessment of how much the payer party should cover (Bouvy & Vogler, 2013), referring to WTP for an additional year in good health.

2.1.1. Uncertainties within Market Introduction

The decision-making process for introducing new medicines takes place under conditions of uncertainty. Problems related to the decision-making process are concerned with the input within the standard reimbursement procedure and can include the quality of evidence, the expected budget impact, the magnitude of effectiveness, and the expected efficiency (McCabe, Stafinski, Edlin, & Menon, 2010). The described problems relate to the three main types of uncertainties on a macro level including uncertainty about the clinical- or cost-effectiveness, budget impact, and the usage of medicines in real-life. At the time of procurement the risk associated to these uncertainties is transferred from the manufacturer to the health care payer (Edlin, Hall, Wallner, & McCabe, 2014).

Ferrario & Kanavos (2013) explain two main ways to address uncertainties related to the assessment of clinical- and/or cost-effectiveness, budget impact, and real-life utilization. The first way collects additional evidence on the effectiveness of a drug, during a specified period of time while conditional reimbursement is granted during this period. In this way, more evidence can be collected about the potential effectiveness of a drug. The second way tries to improve the incremental cost-effectiveness ratio (ICER) of a drug, through decreasing the price, or limiting the utilization of a treatment.

2.2. Managed Entry Agreements Taxonomy

MEAs are no new concept; however, the concept is receiving increased attention in recent years, due to the need to explore new options of reimbursement. Different terms have been used in different contexts to describe the concept of MEAs with among others market access schemes, patient access schemes, and risk-sharing agreements. Defining an MEA is subject to country-specific terms, the context in which they are operated, and different perspectives to what constitutes an MEA (Ferrario & Kanavos, 2015). In 2010, MEAs were defined at the Health Technology Assessment international (HTAi) Policy Forum as:

“An arrangement between a [pharmaceutical] manufacturer and payer/provider that enables access to (coverage or reimbursement of) a health technology subject to specific conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximise their effective use, or limit their budget impact.”

This definition is utilised throughout the thesis as it is described by many others including Ferrario & Kanavos, 2013; Grimm et al., 2016; Klemp et al., 2011. Because an MEA can take

a variety of different mechanisms (e.g. a discount, a price-volume agreement, a price linked to outcome agreement, CED scheme etc.) different taxonomies of to what constitutes an MEA exist in literature. Despite different taxonomies, MEAs can broadly be assigned to two separated categories; arrangements based on (health) outcomes and non-outcome based arrangements (Bouvy & Vogler, 2013; Ferrario & Kanavos, 2015; Grimm et al., 2016). In addition, two types of evidence generation schemes are identified within literature; the category only in research (OIR) and recommended with research (RWR) (Carlson, Sullivan, Garrison, Neumann, & Veenstra, 2010; Grimm et al., 2016; Walker, Sculpher, Claxton, & Palmer, 2012). The two major distinctions in literature are depicted in two frameworks created by Grimm et al. (2016), presented in appendix 1.

Constituting a non-outcome based arrangement, effective prices are determined at a patient or population level (Walker et al., 2012). Arrangements within this category seek to obtain discounts on list prices, based on confidential discounts, price-volume agreements or caps per patient, and are not linked to underlying cost-effectiveness of a treatment (Garrison et al., 2013). However, non-outcome based arrangements are sometimes applied in contexts to affect the incremental cost-effectiveness ratio (ICER) of a medical product. Non-outcome based arrangements can be referred to as financial agreements. Financial agreements are regarded to be relatively easy to manage (Pauwels et al., 2017; van de Vooren, Curto, Freemantle, & Garattini, 2015).

Arrangements based on outcomes link coverage conditions or prices to health outcomes, which are observed in real life, either on a patient or a population level (Garrison et al., 2013). Outcome-based agreements are often divided in coverage with evidence development (CED) schemes and performance-based risk-sharing agreements (PBRSA) (Carlson et al., 2010; Garrison et al., 2013). CED schemes aim to provide evidence regarding decision uncertainty while reimbursement is given for a certain period. PBRSA aim to manage utilization in real-life and control the cost-effectiveness of a drug, as a result it can be discussed how evidence in real life can be translated into revisions in price, revenues and/or use.

OIR involve decisions, which effectively do not recommend a new technology, however reimburse the technology in a study population to generate more evidence for review at a later stage (Grimm et al., 2016). RWR involve decisions who are favourable of funding a technology, but with the condition to conduct more research and a review scheduled at a later stage (Grimm et al., 2016). OIR schemes are considered to be extremely inefficient mechanisms to address uncertainties in evidence, since the value of the information

procedure will typically be much less, than the cost of the scheme unless the degree of decision uncertainty or the budget impact of the technology is small (Edlin et al., 2014). In addition, OIR schemes do not facilitate widespread access to technologies (Grimm et al., 2016).

2.3. MEA Frameworks

Klemp et al. (2011) categorize MEAs according to the nature of concerns they are aimed dealing with respectively managing budget impact, managing uncertainty related to clinical effectiveness and/or cost-effectiveness, and managing utilization to optimize performance. This classification corresponds with a survey conducted by Ferrario & Kanavos (2013) among European Union (EU) member states and Norway. Results demonstrated that 75% of established MEAs were used to address budget impact, either solely for this purpose (42%), or in combination with cost-effectiveness (16%), use (15%), or both (2%). Instruments classified as an MEA, address one or more objectives, where some instruments have an application in more than one area. Bouvy & Vogler (2013) point out that two trends seem to arise in the focus of MEAs across Europe including addressing budget impact, or addressing cost-effectiveness.

Ferrario & Kanavos (2015) developed a conceptual framework to enable an understanding of how MEAs modulate key decision-making variables, shown in figure 1. The framework analyses how MEAs are used in order to influence a set of three intermediate variables. The overall goal is considered improved access to drugs, which is further broken down into two main policy objectives consisting of achieving increased cost-effectiveness, and the limitation of budget impact. In turn, these two objectives will be affected by the three target variables. Based on the application of the framework, Ferrario & Kanavos (2015) argue that in spite of countries stating one objective, such as improving cost-effectiveness, often budget impact is affected as well without direct mentioning. The rationales for MEA implementation across countries are difficult to standardize as a result of confidentiality and data sensitivity Morel et al. (2013).

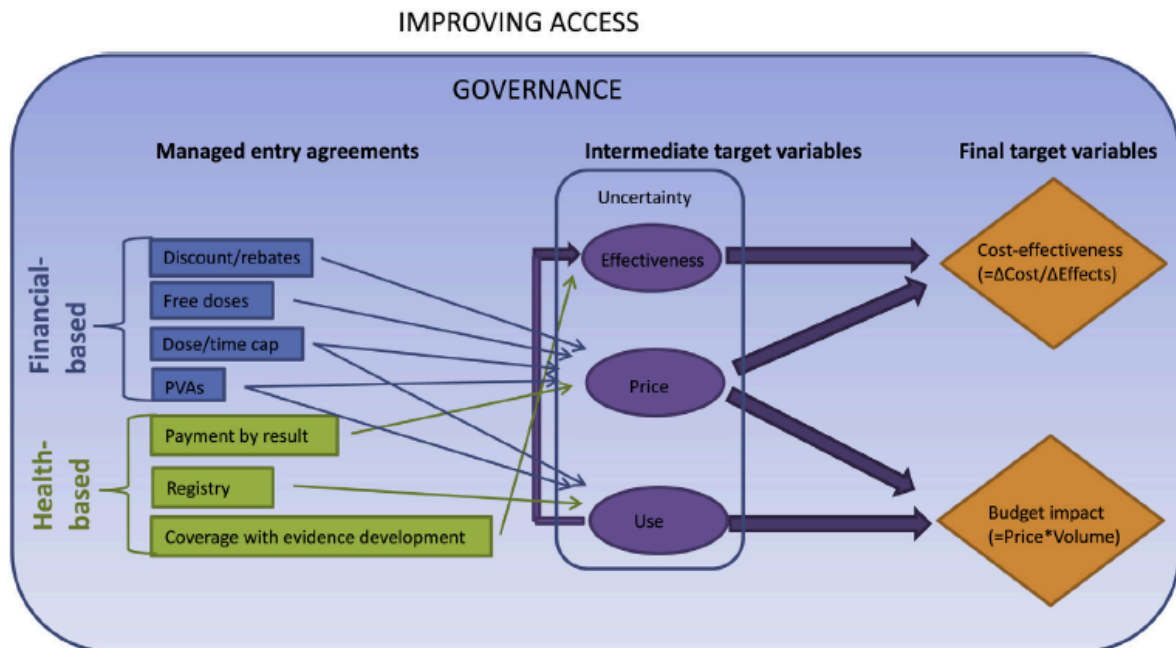


Figure 1. Conceptual Framework for MEAs (Ferrario & Kanavos, 2015).

2.4. MEA as a Contract

The implementation process of an MEA involves the establishment of a contract, which describes the setting of mutually agreed conventions among stakeholders (de Pouvourville, 2006). The specific conventions are specified in national, official regulations (de Pouvourville, 2006). When contracts are established within purchaser-supplier relations, the design and management of the contract can primarily be viewed as an issue of governance and control (Ring & van de Ven, 1992). Selviaridis & Wynstra (2015) argue that in the light of governance and control, especially three theories are worthwhile taking into consideration, including agency theory, management control theory (MCT), and transaction costs economics (TCE).

2.4.1. Agency Theory

The design and establishment of a (risk-sharing) contract can be considered within the framework of principal-agent theory (Zhang, Zaric, & Huang, 2011). Principal-agent theory explains the relationship between principals and agents in a business context (Williamson, 1985). The theory is concerned with resolving problems that can exist in agency relationship due to unaligned goals and/or different aversion levels towards risk. Two types of agency problems are described; a pre-contractual problem and a post contractual problem (Selviaridis & Wynstra, 2015). Economic literature describes models of procurement under conditions of asymmetric information to costs, demand, and both cost and demand (Zhang et al., 2011). Within agency theory, contracts are studied as instruments, used in order to align incentives and share risks Mitnick (1973). Zhang et al. (2011) argue that 'risk-sharing'

contracts have been introduced between pharmaceutical manufacturers and purchasers, in order to assist purchasers with pre-contractual problems. The choice for a contract design is related to the goals and risk preferences of the buyer and supplier (Selviaridis & Wynstra, 2015). Eisenhardt (1989) discusses three variables affecting the effectiveness of a contract including 1) an appropriate measurable outcome, 2) varying objectives between buyer and supplier, and 3) risk aversion from the buyers perspective.

Barros (2011) however, points towards the signalling effect as a role of a risk-sharing agreement. Only firms that have a sufficient degree of trust in their product will enter in an agreement since it is more beneficial for them. This provides further information to a payer party, and will it make easier to make decisions (Barros, 2011). van de Vooren, Curto, Freemantle, & Garattini, (2015) argue that who wins the most of a MEA, depends on how the contracts are “negotiated, designed, and managed.” Although it is pointed out that once a contract has been agreed upon the losers of a MEA contract are likely to be small (van de Vooren et al., 2015).

2.4.2. Managed Control Theory

In the framework of MCT contracts are viewed as coordination mechanisms (Macaulay, 1963). In addition, the theory addresses the choice which should be made between different type of formal controls represented in contractual obligations, and formal organisational mechanisms (Selviaridis & Wynstra, 2015). Two important functions of MCT include the provision of required information for the process of monitoring compliance with contract, and the administration of rewards and penalties (Challagalla & Shervani, 1996).

Managing MEAs, it is recognised that more complex cases, especially agreements involving multiple stakeholders, require a greater need for a formal governance structure in order to ensure transparency of the nature and aims of the scheme, accountability, and function as a mean to mitigate conflicts (Garrison et al., 2013). McCabe et al. (2010) stretches that in order to align objectives of a scheme with the implementation process a form of independent management is required. Consequently, MEAs are depended on governance arrangements.

2.4.3 Transaction of Costs Economics

To achieve efficient economic organization, TCE theory addresses the aligning of transactions with governance structures (Williamson, 1985). Through the alignment of the contract with transaction attributes, the contract is able to efficiently govern the relationship between a buyer and supplier (Argyres, Bercovitz, & Mayer, 2007). TCE suggest that

contracts address behavioural uncertainty through including provisions to safeguard an investment within an agreement, and protect against self-interests of other parties (Kim & Mahoney, 2005).

One of the major concerns implementing a more sophisticated form of MEA is the expected administered burden (van de Vooren et al., 2015). A lack of clarity on what to measure, and how to measure are likely to affect this concern (Menon, McCabe, Stafinski, & Edlin, 2010). Furthermore, challenges in obtaining claw-backs have been reported in literature (Gerken et al., 2017). As a result different levels of complexity in MEAs, however ask for different government structures, and different levels of coordination in contracts (Garrison et al., 2013).

Agency theories have been increasingly tangled with MCT, nevertheless the latter focuses on the management phase of the contract, while the former stresses out the design of a contract (Eisenhardt, 1989; Selviaridis & Wynstra, 2015). TCE complements MCT and agency theory by emphasizing the significance of investment in performance improvement and the costs to administer management systems (Straub, 2009). Agency theory focuses on the core objective of designing a contract, while MCT and TCE focus to streamline the process of a contract.

2.5. Implementation of MEAs

A wide variety of scenarios are available for the choice on different MEA schemes (Grimm et al., 2016). Theoretically there are four major possibilities for payers; to adopt, refusing to adopt until there is sufficient evidence, demand a lower price to reduce the uncertainty about the value, or enter in a outcome-based agreement (Garrison et al., 2013). The choice for the design and implementation of an MEA depends on various characteristics. A variety of frameworks have been considered and developed for evaluating the choice for a specific MEA.

Several principles of good practice have been pointed out including clarity on the decision problem and the objectives, consistency of the design with the objectives of the health care system, and clarity on the governance procedures involved within the scheme (McCabe et al., 2010; Menon et al., 2010). Moreover Garrison et al. (2013) stated that features of good implementation rely on the clarity of the desirability of utilizing an agreement. Walker et al. (2012) developed a conceptual framework consisting of three key futures to make appropriate purchasing decisions regarding new pharmaceutical products. These features

include the expected value of a technology based on the existing evidence, the value of reducing uncertainty about the value of a technology through acquiring evidence, and the value of any investment or reversal costs resulting from an initial positive coverage decision. Whether a specific MEA is desirable is in essence a value of information (VOI) question, comparing the societal benefits of improved resource allocation (Garrison et al., 2013). VOI analysis provides an analytic framework, which can be used to determine the value of acquiring additional information to inform a decision problem (Claxton & Sculpher, 2006).

Grimm et al., (2016) continued with the VOI question of the desirability of MEAs by developing a framework to evaluate the desirability of different MEA schemes. The framework enables to make an informed decision, and as well assess the feasibility of assessing risk in technology appraisals using the payer uncertainty burden of the decisions problem, and the payer strategy burden associated with each strategy. Nevertheless, a scope for further research was identified, which lies in applying this framework on more real-world cases (Grimm et al., 2016). Once the desirability of using an MEA has been determined, there are certain aspects, presented in table 1, which contribute to the appropriate implementation of an MEA.

Table 1. Key aspects affecting appropriate MEA implementation adapted from: (Garrison et al., 2013; Menon et al., 2010).

Aspects influencing 'good' MEA implementation	
1.	Measurement of appropriate outcomes
2.	Acceptable costs, the burden should be in proportion to the benefits
3.	Realistic establishment of a time horizon
4.	Clear funding arrangements
5.	Clear allocation of responsibility for carrying out data collection and analysis
6.	Performance of efficient data collection
7.	Development of evaluation process in order to make revised decisions on price, revenue, or coverage when necessary
8.	Decisions on when discounts/rebates are paid out during the time horizon.

2.6. Review of European Experiences

Literature shows only a limited amount of studies providing evidence on the impact¹ of the use of MEAs. Most studies are descriptive in nature, and discuss the perceived weaknesses

¹ Table 6, appendix 2 presents references studying the impact of MEAs.

and strengths of implemented MEAs (Ferrario & Kanavos, 2015; Gerkens et al., 2017). Table 2 presents a short overview of the perceived strengths and challenges of MEAs based on a review by Gerkens et al. (2017).

Table 2. Strengths & Challenges related to MEA implementation adapted from: (Gerkens et al., 2017).

	Strengths	Challenges
Payers Regulators	<ul style="list-style-type: none"> - Improve access to innovative treatments. Providing a way to reduce uncertainty around the introduction of drugs. - Expands horizon for collecting data. - Influence R&D decisions 	<ul style="list-style-type: none"> - High transaction and administrative costs. - Challenges in obtaining claw-backs - Perspective of irreversibility, difficult to de-list a drug once it has been introduced.
Manufacturers	<ul style="list-style-type: none"> - Improve access to innovative treatments. - Expands the horizon for collecting data. - Incentive for R&D investment. - Price differentiation across countries (especially with financial arrangements). 	<ul style="list-style-type: none"> - Uncertainty about financial rewards for additional produced research. (Could disincentive additional evidence generation). - Issue of free riding with regards to other competitors.
Outcome- Based Agreements	<ul style="list-style-type: none"> - Focus on patients that likely benefit the most from a treatment strategy. - Provides a way of linking health research with decision-making. 	<ul style="list-style-type: none"> - Impact of administrative costs. - Lack of governance structure. - Question of additional evidence, which is necessary. - Lack of clarity on the role of different stakeholders. - Burdensome data collection.
Financial- Based Agreements	<ul style="list-style-type: none"> - Easier to control / Smaller administrative burden. - Containment of costs. - Price Confidentiality (Manufacturer perspective). 	<ul style="list-style-type: none"> - Address the budget, but not the underlying uncertainties to ensure treatment to the right patient group. - Lack of transparency. - Calculations of budget impact and use have proved to be challenging.

One of the aims of this thesis is to provide a country comparison, aiming to explain variations across different countries. There have been several cross section studies published on the

implementation of MEAs² however only a limited amount of studies have been found trying to explain the variations that arise in MEA implementation across countries. Ferrario & Kanavos (2015) explored across four countries the variation in MEA implementation and their governance structures. This research was partly based on a European study performed in 2013, describing the landscape of MEAs implemented across Europe (Ferrario & Kanavos, 2013). Morel et al. (2013) aimed to classify MEAs applied to orphan drugs, and analyse their practice throughout Europe. van de Vooren, Curto, Freemantle, & Garattini (2015) limited a country comparison to Italy and England, describing and assessing the implementation of MEAs within the area of oncology drugs. Pauwels et al. (2017) conducted a similar analysis on the regulation, and application of MEAs within the area of oncology drugs.

Findings presented the different emerging trends with regards to the establishment of arrangements for new costly drugs across over time (Ferrario & Kanavos, 2015; van de Vooren et al., 2015). van de Vooren et al. (2015) showed that where England moved away from implementing performance based agreements towards financial agreements; Italy increased the amount of outcome-based agreement despite the lack of added value of these agreements. Furthermore, Pauwels et al. (2017) pointed out that from 2016 onwards, financial based agreements were the most utilised form in MEA choice for oncology medicines. Studies conducted before 2015, however, show the common implementation of outcome-based agreements (CED schemes) in the Netherlands and Sweden (Morel et al., 2013; Ferrario & Kanavos, 2015).

Within the European survey described in the article of Ferrario & Kanavos (2013) the largest proportion of agreements included drugs with ATC-code L, representing 37% of studied MEAs. The ATC-group L exists of products in the category antineoplastic and immunomodulating agents, including products such as anti-cancer drugs. Considering the study of Morel et al. (2013) this group was as well the largest for orphan drugs. Both Ferrario & Kanavos (2015) and van de Vooren et al. (2015) show only in a minority of cases an MEA applied for the same drug across countries, and the sort of MEA heavily varies. However, with orphan diseases this portion seems to be bigger as nine of 26 studied orphan medicines were subject to an MEA in two or more countries Morel et al. (2013).

The different authors were able to explain to certain extents the variables and conditions causing trends and variations in MEA use within Europe, including the influence of different

² Cross sectional studies on MEAs: Adamski et al., 2010; Carbonneil, Quentin, Lee-Robin, & (EUnetHTA), 2009; Carlson et al., 2014, 2010; Ferrario & Kanavos, 2013; Gerkens et al., 2017; Li, Risebrough, & Hux, 2014; Stafinski, McCabe, & Menon, 2010.

settings and contexts, rapid dynamics in certain disease areas, and the scope of policy setting and legal frameworks (Ferrario & Kanavos, 2015; Pauwels et al., 2017). Nevertheless, further scopes for research across countries were pointed out including differences in risk perceptions, such as differences in WTP and the relative importance of budget impact or cost-effectiveness (Ferrario & Kanavos, 2015).

2.7. Policy Learning

As a result of dynamic, and on-going developments in price mechanisms there is a consequential need for the analysis of pharmaceutical policy (Leopold, 2014). Since countries on a worldwide level are dealing with similar issues regarding the introduction of new high-costs innovative medicine, there is a clear scope to share experiences between countries (Ferrario & Kanavos, 2015). This corresponds with the concept of policy learning. Key aspect to policy learning is learning from multiple organizations, which results in an interaction between collective frames of thinking of different organizations (Kemp & Weehuizen, 2005).

Three types of policy learning, presented in table 3, can be distinguished in order to make policy learning more operational (Kemp & Weehuizen, 2005). Different elements of all three types of policy learning are taking into account within the country comparison.

Table 3. Different forms of policy learning (adapted from Kemp & Weehuizen, 2005).

Type of policy learning:	
Instrumental Learning	Technical learning how instruments may be improved to achieve set goals.
Conceptual Learning	To develop or adopt new concepts, when viewing instruments from a different perspective.
Social Learning	Improving instruments when learning from values of significant properties, such as responsibilities, norms, objectives, and the framing of causes.

Chapter 3. Research Methods

Chapter three provides a general outline of the conducted methodology, and discusses the used research philosophy, followed by the research approach, research strategy, data collection techniques, analysis of the data sources, generalizability, and ethical considerations.

3.1. Research Philosophy

Different research philosophies take different approaches to the creation of knowledge. Defined by Saunders, Thornhill, & Lewis (2009) as “the development of knowledge and the nature of knowledge”, a research philosophy reflects the assumptions of an author, which establish the base for a research strategy. The importance of a research philosophy can be indicated through four different stages (Rubin & Rubin, 2012). In the first stage, a research philosophy will help understand the nature of the research, and provide guidance in what to do. Second, it will help to understand the choice for a chosen method for the research. Third, a research philosophy gives a standard for evaluating the quality of a research project. Lastly, by understanding the philosophy, the researcher will be better able to understand the theoretical assumptions underlying a research setting and therefore be more exploratory in nature.

The conducted research takes an interpretivist³ approach, as this study sets out to understand how stakeholders interact in a specific context. Researchers taking an interpretivist approach integrate the human interests into a study and assume that reality takes place through the development of social constructions such as language consciousness, shared meaning and instruments (Myers, 2008). From this philosophy it is important for a researcher to act as a social actor to appreciate the differences between people and contexts as social phenomena are in a constant state of revision (Saunders et al., 2009). Furthermore, the managerial situations that are studied (establishment of an MEA between different actors, and within different settings) are highly complex in nature; therefore, it is more difficult to generalize, which excludes for example the often-used positivist approach. Generalisation takes place through theoretical abstraction. In addition, this approach is often used in qualitative research, where small, in depth-samples are involved in order to understand human interaction. However, it can be argued that elements

³ Four types of philosophies are distinguished in literature including pragmatism, positivism, realism and interpretivism (Saunders et al., 2009; Thomas, 2004). For more information see appendix 3.

of a pragmatism philosophy are taken into account as it is recognised that a single perspective only cannot provide an appropriate overview. Therefore, three different countries are included within the country comparison.

3.2. Research Approach

Two broad methods of reasoning, used in social science research, are a deductive and an inductive approach. A deductive approach is characterized as a top-down approach that starts with existing theories and frameworks that can be narrowed down in a hypothesis to test. Contrarily, an inductive approach is characterized as a bottom-up approach. This method initiates with making specific observations resulting in formulating generalizations applicable to an extended context. An inductive approach is inclined to study smaller study samples than that of a deductive approach, and is therefore more likely to be linked with a qualitative design (Saunders et al., 2009). Nevertheless, it has to be noted that the two approaches are not mutually exclusive, as elements from both approaches can be used (Saunders et al., 2009).

The performed research is inductive in nature as the thesis sets out to study a specific situation in both the country comparison as in the interviews. Specific elements of health care systems and pharmaceutical policies in three countries are studied, in addition to the gathering of perspectives from different stakeholders within the process of pricing and reimbursement. In this way, a broader view of the MEA and stakeholder landscape will be established on both a European and Norwegian level. As a result, certain generalizations will be made through theoretical abstraction.

3.3. Research Strategy

To achieve the objective of the thesis, the performed study is of qualitative nature. This strategy has been chosen due to the need for a more detailed understanding of the use of MEAs in different countries and the perceptions towards MEAs in Norway. It aims to develop an understanding of a social problem from multiple perspectives. Qualitative research builds a complex and holistic picture of a phenomenon of interest. A qualitative method involves the systematic collection, organisation, and interpretation of textual material (Malterud, 2001). Several patterns occur from the data analysis through conceptualization (Saunders et al., 2009).

The performed research can be divided within two parts; a country comparison and interviews. Through triangulation among different sources, information is gathered. The

country comparison is applied because of the emergence of a transnational issue, the high uncertainty related to the introduction of high-cost medicine. Within social sciences a comparative method refers to methodological issues arising within the systematic analysis of a small number of cases (Collier, 1993).

The second part of the research is based on interviews. Patterns of interest often emerge from informants; therefore the researcher often interacts with those being studied. Interviews are based on the discussion between two people, and used to gather valid and reliable data relevant to the research area (Saunders et al., 2009). This part of the research strategy will be based on semi-structured interviews. Conducting semi-structured interviews, an interviewer has an interview protocol where key themes and issues are defined in advance. Nevertheless, conducting semi-structured interviews leaves room for unstructured aspects as well, since there is room to deviate from the established standard interview protocol. The interview protocol for the conducted interviews can be found in appendix 5.

3.4. Research Procedure

This paragraph will discuss the different data gathering techniques and procedures used to conduct the research.

3.4.1 Data sources

The literature within the theoretical framework is used due to its reflective nature to put the findings of the research in context. To find relevant publications for inclusion within the theoretical framework different search strategies were used. First, references were searched through electronic bibliographic databases including Google Scholar and Science Direct. Used searched terms included *'managed entry agreements'*, *'patient access schemes'*, *'uncertainty'*, *'conditional coverage'*, *'access with evidence'*, *'coverage with evidence'*, *'performance-based risk-sharing'*, *'risk sharing agreements'*, *'pharmaceutical risk-sharing'*, and *'cost-effectiveness'*. A second used strategy is the ancestry approach, which can also be referred to as pearl growing. This approach tracks down references used in relevant studies (Cooper, 2010).

For the country comparison, three countries were included. The Netherlands, England (and Wales), and Norway were chosen due to the availability of material, their procedure of involving HTA in the process of marketing authorization, and language considerations. The gathering and examination of documents is often a key element in qualitative research (Bryman, 1989). Analysis of documents can fulfil a number of functions such as the collection of information which cannot be properly addressed through other research methods, it can

contribute a different level of analysis from other methods, and check the validity of information derived from other methods (Bryman, 1989). Sutton (1987) points out that multiple documents can be employed in document analysis such as marketing research on attitudes, budgets, internal correspondence, financial viability study by consulting firm, newspaper articles, and press releases. These sources were used in addition to country specific reports, internet websites, and existing academic literature about MEAs in those countries.

For the purpose of this research, five interviews were conducted. Participants have been recruited based upon their expertise in the field of the introduction of high cost medicine, including pricing and reimbursement, market access, and regulatory affairs. In order to get a clear view of the current landscape, employees from different stakeholders have been contacted including pharmaceutical manufactures represented in Norway, policy regulators, HTA bodies and organizations with political influence. Table 4, shows a profile of the different participants, including a code, which is utilised in order to represent the participants in the data analysis. The presented table is limited in its information as a result of privacy protection.

Table 4: Overview of interview participants.

Interview	Code	Background	Subsector
Interview 1	INT1	Health Economist	HTA
Interview 2	INT2	Economist	Pharmaceutical industry
Interview 3	INT3	Medical doctor / Business Economics	Procurement
Interview 4	INT4	Health Economist	Pharmaceutical Industry
Interview 5	INT5	Pharmacy / Politics	Politics

3.4.2 Data analysis

The data was analysed by performing a thematic analysis. Analysing text involves four key tasks, including discovering themes and subthemes, subtraction of the important themes to the project, establishing hierarchies of the themes, and connecting the different themes to the theoretical models (Ryan & Bernard, 2003).

Saunders et al. (2009) describe specific procedures prior to setting-up a qualitative analysis, consisting of first the classification of data into specific categories, based on the collected data or the established theoretical framework. Second, the categories have to be labelled in order to align a description with these themes. Third, the generation of relationships occurs as a result of finding themes and patterns in the data.

The analysis of the country specific data was performed according to these procedures (Ryan & Bernard, 2003; Saunders et al., 2009). Data was classified into specific categories based on the literature presented in the theoretical framework. By applying a thematic analysis, the qualitative data could be quantified according to the different concepts. By combining fragments of similar information across the different countries, the themes were able to provide a sufficient understanding of the bigger picture (Attride-Stirling, 2001). In addition, simple descriptive statistics were performed in Excel to analyse the use of MEAs.

Data gathered from the different interviews, was analysed in a similar manner. Data recorded on tape were transcribed into transcripts in order to find concepts and patterns in the answers given by the respondents. The retrieved data was labelled into important categories, selected in advance of the analysis and based on the theoretical concepts and frameworks. Concepts were marked in the text and units of data were attached to the several different categories. As a result, a clear overview of all the topics was given across all five interviews. In addition, relations were generated from the findings by seeking for themes and patterns in the data.

3.5. Quality of Research Method

Validity and reliability have often been a key issue in the discussion about the legitimacy of qualitative research, since qualitative research is based on a presentation of data, retrieved from an interpretation of events, generalization of study finding is questioned (Maxwell, 1992; Morse, Barrett, Mayan, Olson, & Spiers, 2002). Nevertheless, the need for a quality check or measure to validate the research is recognized (Golafshani, 2003).

3.5.1 Validity

Internal validity refers to whether a study investigates what it is ought to investigate, whereas external validity refers to context in which finding of a study can be applied (Malterud, 2001). Whilst in quantitative research, credibility depends on the construction of different instruments, in qualitative research the researcher functions as the instrument (Patton, 2002). To assure both the research process and results of a high rigor and robustness, every step of the research process, from the theory formation to forming conclusions, has to be validated on transparency and a systematic manner of working (Leung, 2015).

To assure that the research functioned as a reliable instrument, the data gathering and analysis considering documents and literature has been performed in a systematic procedure described previously in paragraph 4.3. Only when working in a transparent and systematic

way findings can be shared with others. Furthermore, with regards to the interviews several types of biases were taken into account, including interviewer bias and response bias (Saunders et al., 2009). To overcome these forms of bias a transparent approach has been taken including sending an appropriate level of information to interviewees, having an open-minded attitude during the interview and the accurate and reliable recording of the data.

One of the aims of research is to generate findings and information that can be shared and applied beyond the setting of a specific study (Malterud, 2001). This can be referred to as transferability. The performed study aims to study how countries cope with the introduction of high-cost medicine surrounded with uncertainty and the implementation of MEAs in a European landscape. After comparison, these findings are partly generalized to draw lessons, what Norway can learn from these contexts. Concerning the interviews, aspects of the external validity could be questioned due to the small number of interviews. On the other side, the interviews serve as a case study and therefore create an in-depth picture of this process of the broader industry.

3.5.2 Reliability

Reliability can be a challenge within qualitative research due to the diversity of used paradigms (Golafshani, 2003; Leung, 2015). It is argued that since reliability concerns the issue of measurement, it has no relevance to qualitative research (Stenbecka, 2001). Lincoln & Guba (1985) and Patton (2002) on the other hand state that the occurrence of reliability is a consequence of the validity of a research. Therefore, to ensure reliability in qualitative research, the trustworthiness of a study is essential (Golafshani, 2003). Leung (2015) further points out that the essence of reliability lies within the consistency of a study.

The performed semi-structured interviews were not only used to influence the direction of the discussion, but as well to ensure that there is a consistency across the different interviews with regards to the different concepts. In this way, a more reliable basis for comparison was created.

3.6. Ethical Considerations

In order to protect the privacy of all involved participants, several ethical considerations have been taken into account. All respondents taking part in the interviews have been treated in an anonymous way, in order to ensure their privacy and to provide them with the opportunity to express thoughts openly to the researcher. All participants had to sign an informed consent before the start of the interview, which guaranteed their anonymous character,

appendix 4. The informed consent was accompanied with an information letter, which informed the participants about the voluntary nature of taking part in the research, the option to have the interview audio taped, and their option to withdraw from taking part in the research at all time without any consequences.

Data retrieved through the interviews, including audio records and transcript records will be stored on password-protected systems. Interviews are recorded on a iOS smartphone, and the audio file will be stored on the internal memory of the smartphone locked behind a pin code protected entry, until transferred to a password-protected laptop. Data will be destroyed when the final thesis grade is awarded.

Furthermore, the project has been registered at Personvernombudet For Forskning (Privacy ombudsman for research), the Norwegian centre for research data because, according to Norwegian rules and regulations, appendix 6. This was required because participants were involved within the study.

3.7. Methodological Limitations

Methodological limitations imply the characteristics of the chosen methodology or design that impact the findings of a research (Price & Murnan, 2004). Characteristics including constraints towards the generalizability, applications to practice, and/or utility of findings that are the result of the ways in which a researcher initially chooses to design the study and/or the method used to establish internal and external validity (Price & Murnan, 2004).

As in qualitative research, the researcher functions as the instrument, the background and position of a researcher will affect what is chosen to investigate, the angle of investigation, and the chosen methods judged to be the most adequate for the purpose (Malterud, 2001). It has to be recognized that the perspective of an observer is limited in its being and determines what can be observed (Haraway, 1991). The researcher had only a limited amount of experience within the field of conducting semi-structured interviews. This issue was addressed through getting acquainted with different existing guidelines and protocols for interviewing⁴. Nevertheless, looking back certain follow-up questions would have been asked.

⁴ The following sources were consulted for information about interview guidelines and protocols: Leech, 2002 and Rubin & Rubin, 2012.

The time horizon of the thesis was of a limited nature, therefore only a certain amount of interviews could be conducted, and a precise selection of participants had to be made. In addition, access might be a limitation, as not all persons invited to take part in the research responded to this request. In addition, only a limited amount of countries could be included within the country comparison. As a result, findings could only be generalized to a certain extent.

Last, qualitative research represents collecting large amounts of information; therefore, errors in data collection and interpretation have to be recognized. To overcome this, first of all this presumption of qualitative research was kept in mind. In addition, a systematic manner of collecting and analysing the data was utilised to attempt reducing the systematic bias.

Chapter 4. Country Comparison Analysis

The results section of the country comparison provides an analysis of concepts related to MEAs within three countries including the Netherlands, England (and Wales), and Norway. These countries have been chosen based on language considerations, availability of data and policy documents, and varying healthcare system characteristics.

The analysis simply indicates key findings of the different concepts retrieved through the theoretical framework. Key findings are presented in boxes at the end of each paragraph, and further discussed within chapter six. Variables that have been analysed in the country comparison include: Reimbursement Mechanisms, Managed Entry Agreements, Legal Frameworks, Rationales for the use of MEAs, Characteristics of MEAs, and Implementation Processes.

4.2. Reimbursement of Drugs

4.2.1. Norway

The Norwegian health care system is organized from the underlying principles of equal access to services for the whole population, with as key characteristic the predominance of tax-financed public provisions (Håkonsen & Andersson Sundell, 2015; Ringard, Sagan, Sperre Saunes, & Lindahl, 2013). The Ministry of Health and Care Services (HOD) serves as the legislative authority, and is responsible for setting policy, legislation, and national budgeting. Norway is divided within four regional health authorities (RHAs), which manage the hospital trust for that region (Ringard et al., 2013). Membership to the national insurance scheme is mandatory for all citizens, and contributed through via taxes. Coverage through the insurance scheme is managed by the Norwegian Health Economics Administration (HELFO).

Pricing and regulations of pharmaceuticals are strictly regulated. The Norwegian Medicine Agency (NoMA), subordinate to HOD, is in charge of marketing authorisation, classification, vigilance, pricing, reimbursement, and providing information on medicines to prescribers and the public (Statens Legemiddelverk, 2016). The regulations for the marketing of pharmaceutical products are corresponding and harmonized with relevant EU regulations (PPRI, 2015).

Both outpatient and inpatient medicines are evaluated for reimbursement by NoMA in order to assess whether these medicines are eligible for reimbursement. Moreover, NoMA establishes the prices for outpatient medicines. The medicines approved for reimbursement are included in the 'blue list', and are financed partly through co-payments, and partly by HELFO as part of the insurance scheme.

Different than for outpatient medicines, the main pricing policy for inpatient pharmaceutical products consist of the tendering mechanism for drug procurement (PPRI, 2015). The Norwegian Drug Procurement Cooperation (LIS⁵), coordinates the tendering process, which aims to reduce the cost of expensive treatments and therefore negotiates prices on behalf of the hospitals (Mielnik, 2014; PPRI, 2015). As stated in § 1 of the LIS regulations: "The purpose of the Drug procurement cooperation (LIS) is to prepare the basis and specifications for purchase and delivery agreement of pharmaceuticals in cooperation with the state owned hospitals, and thereby reduce the costs" (Mack, 2015). Inpatient medicines are free of charge to patients, and are covered through the budgets of respectively the RHAs and municipalities (Ringard et al., 2013).

4.2.2. The Netherlands

The Dutch health care system can be characterized as a hybrid system, incorporating a blended system of social health insurance, shared governance among health insurers and professional organizations, and elements of regulated competition (Kroneman et al., 2016). Participation in a basic health insurance scheme is mandatory, and contributed to through premiums. Different health insurers are responsible for managing the coverage of these schemes. The government establishes the budget of health, and decides on the content of the basic health benefit package (Kroneman et al., 2016).

The Dutch Minister of Health decides whether a drug should be eligible for reimbursement covered through the basic health benefit package, based on advice and assessment provided by the Dutch Health Care Institute (ZIN). ZIN advises whether outpatient and inpatient medicine are eligible for reimbursement through the benefit package (ZIN, 2017).

Outpatient medicines are reimbursed when included in the medicine reimbursement system (GVS). Specialist inpatient care enrolls automatically; as a result, these medicines will be directly eligible for reimbursement at the moment of market registration. Inpatient

⁵ Legemiddelinnkjøpssamarbeid (LIS), merged in 2015 with HINAS, LIS operates as the divisjon legemidler, however is still often mentioned as the former LIS.

pharmaceutical care is included and reimbursed via bundled payment reimbursement. Nevertheless, specialist health care which is considered to be a threat for the affordability is assessed in the context of 'risk-oriented package control' (Pasman & Dupree, 2013). This approach is applied on medicines with an estimated budget impact of at least €2,5 million or more. A couple of medicines in the past have been lifted from outpatient to the care of the hospitals such as TNF inhibitors, growth hormones, and all cancer medicines (Kroneman et al., 2016).

4.2.3. England

The health care system of England is largely funded through taxes, collected and pooled at the United Kingdom (UK) level (Cylus et al., 2015). The UK government directly decides on the policy of the National Health Service (NHS) in England. The Department of Health functions as the legislative authority and provides national policies for financial control, and delivery and performance of the NHS (, 2017). All legal citizens can make use of the services provided through the NHS, in addition to the right to purchase private health insurance if they wish to (Cylus et al., 2015).

The Pharmaceutical Price Regulation Scheme (PPRS) is a voluntary, non-contractual agreement negotiated between the government and the Association of the British Pharmaceutical Industry. The agreement controls the pricing of all licensed drugs sold to the NHS throughout England. The aim of the scheme is to ensure that the NHS can obtain drugs at a fair price, while promoting a strong industry. The PPRS places a limited on the profits individuals can earn from supplying medicines to the NHS, while allowing a return on capital within certain limits. The scheme originating from 2009 was updated in 2014, and sets in place flexible pricing⁶, and patient access schemes (Department of Health, 2013). These two mechanisms are applied to ensure an improved reflection of value. The National Institute of Clinical Excellence (NICE) is a non-departmental body responsible for the development of guidelines and reviewing the clinical- and cost-effectiveness of pharmaceutical products and other health interventions (Ferrario & Kanavos, 2013).

Purchasing decisions about medicines are made at a local level, given budgetary constraints (Cylus et al., 2015). Third party purchasers are not obligated to include medicines or other interventions, which have been proven to be cost-effective in the package of benefits locally. Similarly, they are also in a free position to cover interventions, which appear to be not cost

⁶ Flexible Pricing: A manufacturer can apply for an increase or reduction in the original list price, as a result of new evidence or additional indications being developed (Department of Health, 2013).

effective. However, this led to complaints concerning geographic inequality, as some areas will cover certain services or treatments, which are not available in neighbouring regions (Cylus et al., 2015). Therefore, NICE, ought to develop guidelines in the area of HTA to improve this equality (Cylus et al., 2015; Ferrario & Kanavos, 2013).

The variety in different health care systems, and the economic affluence of individual countries, results in heterogeneous methods of price setting and reimbursement within different European countries (Edlin et al., 2014; Pauwels et al., 2017). Within all three countries, an advisory body carries out a form of HTA, to provide guidelines on the eligibility for reimbursement.

4.3. Managed Entry Agreements

4.3.1. Norway

According to WHO Collaborating Centre for Pricing and Reimbursement Policies, PPRI (2015) MEAs⁷ are not in place in the out-patient sector in Norway. This corresponds to the survey performed by Ferrario & Kanavos (2013), concluding that Norway has had limited experience with MEAs in the past (two agreements are indicated), however are currently not in place or implemented. One example of an MEA was the establishment of a CED scheme for the reimbursement of Sunitinib to treat renal cell carcinoma (Grepstad Lundebj, 2014).

Nevertheless, discounts are not uncommon in Norway. Discounts are often initiated and negotiated between a pharmaceutical manufacturer and the procurement cooperation (LIS), within the purchasing process of inpatient medicines. Other discounts initiated than in the price negotiations are not common (PPRI, 2015). Discounts in the MEA taxonomy are described as *“The negotiated price differs from the list price”* (Grimm et al., 2016). In turn, it can be argued that despite a lack of literature on MEAs, these instruments are applied within Norway.

⁷MEAs in this thesis are defined as “An arrangement between a [pharmaceutical] manufacturer and payer/provider that enables access to (coverage or reimbursement of) a health technology subject to specific conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximise their effective use, or limit their budget impact” Klemp et al., 2011.

4.3.2. The Netherlands

Two types of agreements are identified in literature and Dutch policy documents. The first type consists of outcome-based agreements, with a specific focus on CED schemes. The second type constitutes financial arrangements.

In 2012, a pilot was started with the implementation of financial arrangements. A financial arrangement is established as a contract between the government and the pharmaceutical company, where a price decrease is central to the agreement (Ministerie van Volksgezondheid, Welzijn en Sport, 2014). The arrangement can take different forms such a price/volume agreement or another form of discount.

In the past, a CED system was introduced for expensive hospital drugs (2006-2011). From 2012 onwards, this system for reimbursement of inpatient medicines was replaced. The new policy combined a system of conditional financing (CED schemes) and risk-oriented package control (Pasma & Dupree, 2013). From 2014, this policy was extended to outpatient medicines. Potential promising medicines in this policy can be admitted to the benefit package, on certain conditional terms. These conditional terms include that manufacturers have to collect additional information regarding the clinical effectiveness and/or cost-effectiveness of a drug. The policy expanded the choice of decisions the Minister could take about the reimbursement, with a yes, if conditional evidence is collected (Pasma & Dupree, 2013).

There has been some experience, with the application of performance-based agreements, such as a pay for performance scheme for Xolair to treat severe asthma. Nevertheless the system of MEAs has been under reform since 2016, which resulted in the discontinuation of outcome-based schemes, including CED schemes (Gerkens et al., 2017; Pauwels et al., 2017). ZIN gave the following reasons for the discontinuation of CED schemes: *“Usually there was already sufficient evidence at the moment of market authorisation to conclude that the pharmaceutical was not cost-effective or there was no necessity to collect additional data for 4 years to prove cost-effectiveness”* and *“It is not legally required to deliver evidence on cost-effectiveness reimbursement decisions* (Gerkens et al., 2017).

4.3.3. England

In England, the concept of an MEA is better known as a Patient Access Scheme (PAS). PAS schemes were first introduced in 2007 (Ferrario & Kanavos, 2015). PAS schemes are regulated subject to the PPRS of 2014. PAS involve innovative pricing agreements designed

to improve cost-effectiveness and facilitate access to specific drugs and technologies (NICE, 2009).

The typology set out by the PPRS set out two forms of PAS schemes consisting of simple discount schemes, and complex schemes (Department of Health, 2013). A simple discount must meet the criteria of not imposing any significant burden to the NHS. This can be realised in the form of a discount or a reduction on the list price. To the PPRS and the Ministry of Health, a simple discount is the preferred model due to the fact that these agreements incur the least burden on the NHS and manufacturers. Complex schemes include all other possible types of PAS schemes such as rebates, dose-capping schemes, or outcome-based schemes.

Within all three countries, at least one form of an MEA is utilised. Nevertheless, taxonomies differ between the three countries, where different terms and policies are utilised for the implementation of such instruments.

4.4. Legal basis for the use of MEAs

4.4.1. Norway

The general legislation on pharmaceuticals includes several provisions, pointing to the possibility to use MEAs as an instrument within the reimbursement process. It is stated that discounts resulting from an agreement between the public, and the drug's right holder to ensure public funding of the drug are allowed Lov om legemidler of 1992, §6 (Helse- og omsorgsdepartementet, 1992)). In addition, this act was extended in 2016 with a provision stating that an agreement between the public and a drug's licensor may enter into a refund agreement on public funding of a medical product Lov om legemidler of 1992, §6 (2016) (Helse- og omsorgsdepartementet, 1992). The agreement may stipulate that the licensor of a product, shall, in full or in part, refund the public's expenses as a result of the prescribing of the drug to more patients than prescribed, or provisions that otherwise reduce the public spending. Furthermore, the contract ought to have rules on how parties can assume responsibility after the termination of the contract. This extension of the law indicates that payback schemes are legally allowed as a form of reimbursing medicines, since 2016.

4.4.2. Netherlands

The Dutch Minister of Health is legally entitled to refuse or exclude interventions from the benefit package if these appear to be not cost-effective (Ferrario & Kanavos, 2013). The

financial arrangements do not fall within a specific legal framework (Ecorys, 2016). The arrangements function as an instrument to control costs alongside other policy instrument such as the law on medicine prices, the reimbursement systems for medicines, and the guidance on medical specialist health care 2014-2017 (Ecorys, 2016; Kooijman, 2016). Nevertheless, an evaluation of the financial arrangements commissioned by the Department of Health, stated that the position of the financial arrangements within the health care system is not clear all the time among stakeholders (Ecorys, 2016).

4.4.3. England

In England there is no specific legal framework in place for the use of MEAs or PAS schemes (Ferrario & Kanavos, 2013). However, the guideline of the PPRS of 2014, functions as a clear policy basis for the set-up and implementation of PAS schemes.

Two of the three countries have a legal framework in place, which steer the decision-making process of MEAs.

4.5. Rationales for the use of MEAs

4.5.1. Norway

Policy documents or literature on the specific implementation or use of agreements classified as an MEA are lacking in Norway. Nevertheless, within the process of tendering inpatient medicines, the aim is to reduce costs of expensive treatments (Mack, 2015; Mielnik, 2014). Priority criteria used to assess the eligibility for reimbursement of potentially beneficial products include the cost-effectiveness in order to achieve the highest possible health status for the costs invested, the severity of the disease, and the effectiveness of the drug on the treated patients (Statens Legemiddelverk, 2017).

If an ICER of a new potential product is not regarded to be cost-effective by the Norwegian standards, discounts can be initiated to reach a more favourable ICER. In order to address the uncertainty related to the clinical and/or cost-effectiveness, a model is utilised by decreasing the price of a treatments to improve the ICER as a result of lower costs.

In 2015 a white paper on the principles for prioritization of health care services was published (Helse- og omsorgsdepartementet, 2015). The paper sets out the existence of WTP thresholds, however these are not publicly available. The WTP for a specific treatment is

related to the severity of the disease, which is also assessed as a priority criterion to evaluate the eligibility for reimbursement.

4.5.2. The Netherlands

The CED policy aimed to ensure access to medicines, which might not have sufficient evidence according to the 'state of science' (Staal & Schelleman, 2016). In order to address uncertainty related to the clinical- and/or cost-effectiveness a model is utilised through granting conditional reimbursement, for a limited period of time. This model targets the underlying uncertainty of clinical-, and cost-effectiveness. During the conditional time period, additional evidence on the effectiveness of the drug has to be collected in order to update the reimbursement decision based on new cost-effectiveness results (Ferrario & Kanavos, 2015; Staal & Schelleman, 2016).

Base to financial arrangements is to decrease the price or the macro budget impact of effective, innovative medicines, in order to make an affordable inclusion of the drug within the benefit package possible (Ecorys, 2016). The minister is advised to consider a financial arrangement with a pharmaceutical company for two reasons: 1) there is an unfavourable ICER, or 2) if there is a (above average) high budget impact (Ecorys, 2016; Ministerie van Volksgezondheid Welzijn en Sport, 2016b). Therefore, in this case a model is utilised to address uncertainty by decreasing the price or limit the utilization of a medicine, in order to improve the ICER.

With the assessment of cost-effectiveness of new drugs, WTP reference values are handled from 10.000 up to 80.000 per QALY (Zwaap, Knies, Meijden van der, Staal, & Heiden van der, 2015). However, it can be justified to use higher cost per QALY under certain circumstance, such as a high disease severity. The higher the severity of a disease, the higher reference values are taken into account and vice versa.

4.5.3. England

PAS schemes are introduced as an additional pathway to ensure access to cost-effective, innovative medicines (Department of Health, 2013). The medicines are likely to have a too high cost, and might not be deemed as cost-effective by payers. A common model used to address uncertainty in England, is by decreasing the price or limit the utilization of a medicine, in order to improve the ICER because of lower costs (Ferrario & Kanavos, 2013).

Assessing cost-effectiveness of new drugs, NICE handles reference values with a WTP of maximum 30.000 pounds per QALY (Ferrario & Kanavos, 2013). These criteria only apply, when no end of life criteria are applied. There are certain methods available in England, which allow a higher WTP per QALY, such as if a diseases falls within end-of-life criteria. The WTP for end-of-life criteria is not publicly established, however there are indications that the threshold lies around 50.000 pounds per QALY (Stewart, Eddowes, Hamerslag, & Kusel, 2014). Nevertheless, the end-of-life criteria established by NICE, are part of a different policy than the PAS schemes.

Similar types of uncertainties are addressed in all three countries. The framework developed by Ferrario & Kanavos (2015) presented in figure 1, contributes to explaining the different rationales underlying MEA implementation. A tendency to use models aiming to address uncertainty through lowering the price to favour the ICER is prevalent. Both budget impact and cost-effectiveness are affected through this model. Furthermore, two of the three countries have publicly established WTP thresholds.

4.6. Characteristics of MEAs

4.6.1. Norway

As MEAs are not recognised as such in Norway, no publicly available data on MEAs was found. Paragraph 4.3.1. and 4.4.1 highlight in what way MEAs are currently applied in Norway.

4.6.2. The Netherlands

In June 2017, 12 interventions were included in the basic health benefit package as part of the conditional financing policy (Zorginstituut Nederland, 2017). Two of these interventions were identified as a drug. The other interventions include other types of care such as surgery. One drug is included since 2015 and is to be reviewed in 2019, and one drug is included since 2016 and is to be reviewed in 2018. The therapeutic disease areas include a drug for multiple sclerosis (ATC-code N), and a drug for Systemic Lupus Erythematosus (ATC-code L).

In 2016 there were nineteen financial arrangements in place for as well outpatient as inpatient medicines (Ministerie van Volksgezondheid Welzijn en Sport, 2016a). In comparison, at the beginning of the start of the pilot in December 2012, there were only two

financial arrangements in place (Ministerie van Volksgezondheid Welzijn en Sport, 2016a). Figure 2, presents the different types of arrangements implemented in the Netherlands. Not all types of arrangements could be identified as a result of lacking data or confidentiality.

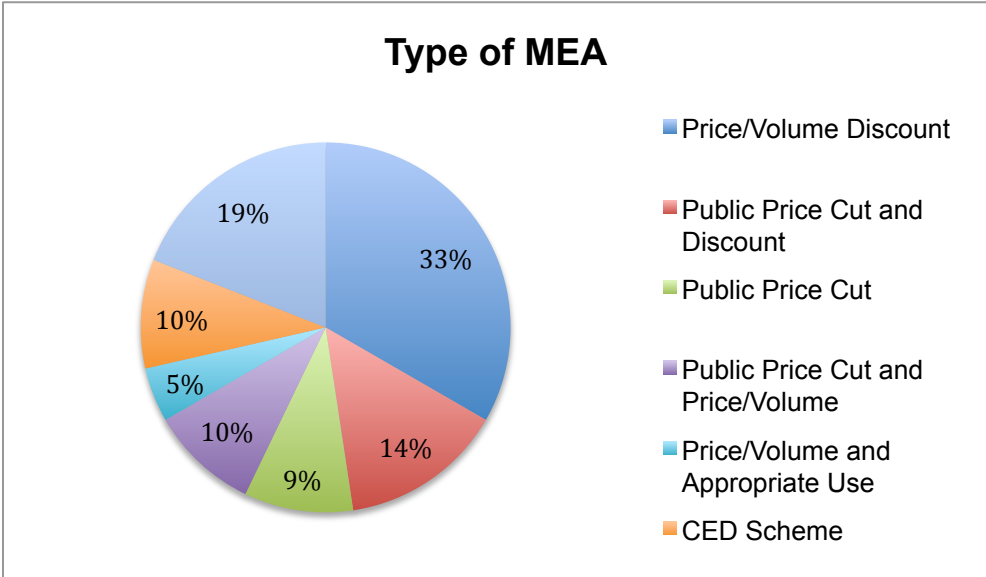


Figure 2. Types of Arrangements in the Netherlands, own presentation adapted from Ministerie van Volksgezondheid Welzijn en Sport, 2015 & “Officiële bekendmakingen: Zoeken,” n.d.⁸

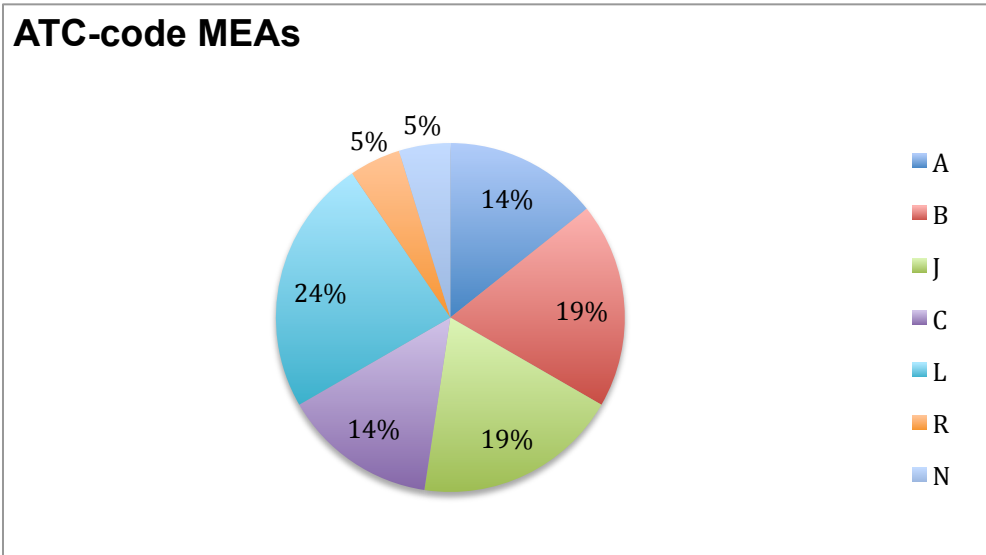


Figure 3. Therapeutic Focus of MEAs in the Netherlands, own presentation adapted from: (Ministerie van Volksgezondheid Welzijn en Sport, 2016a) & (Schelleman, 2017).

The three largest therapeutic areas are ATC-L, ATC-J, and ATC-B, which include some of the innovative medicines in cancer medicines, chronically Hepatitis C medication, and New

⁸ ‘Officiële bekendmakingen’ includes official announcements by the Dutch Government.

Oral Anticoagulants (NOACs). Some medicines, such as the cancer medicine Nivolumab, part of a financial arrangement, include financial arrangements for all registered indications attached to that specific medicine. Figure 3 shows an overview of the therapeutic disease areas, which have been targeted with the two different MEA policies.

4.6.3. England

In May 2017, 113 PAS schemes were identified on the website of NICE⁹. This total amount of 113 PAS schemes included 23 pharmaceutical products with two or more indications, making up 62 of all PAS schemes. In total for 51 pharmaceutical products, one or more PAS schemes have been applied. Figure 5 presents the different types of PAS schemes applied in England. 93 of the indicated PAS schemes exist of a simple discount (82%).

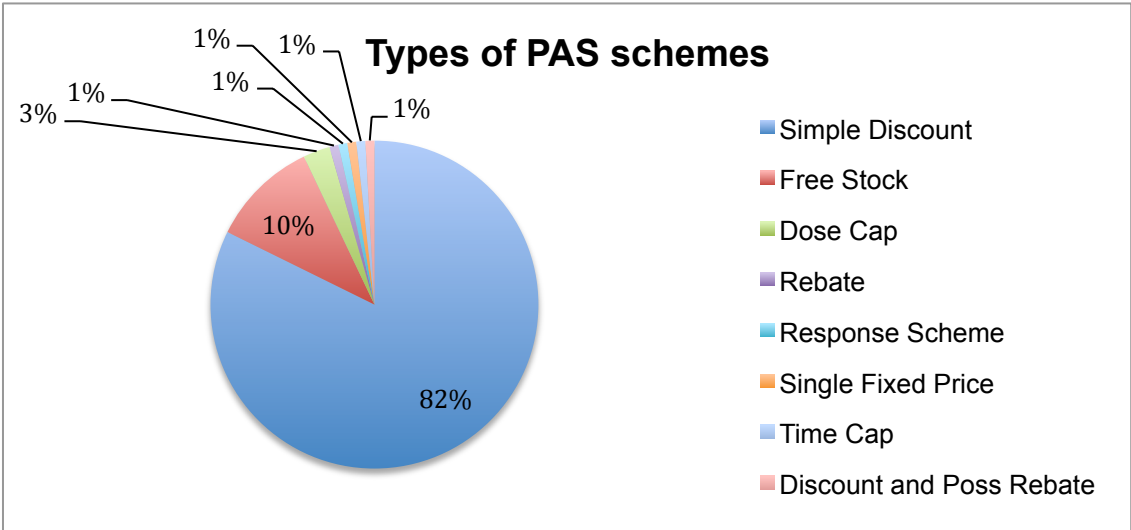


Figure 4. Types of PAS schemes in England, own presentation based on the list of technologies approved with Patient Access Schemes, by NICE.

Figure 5, shows an overview of the therapeutic disease areas, which have been targeted with the introduction of the PAS schemes. 76% of all PAS schemes are focused on a drug in the therapeutic area with ATC-code L.

⁹ List of technologies with approved Patient Access Schemes available on <https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit/list-of-technologies-with-approved-patient-access-schemes>

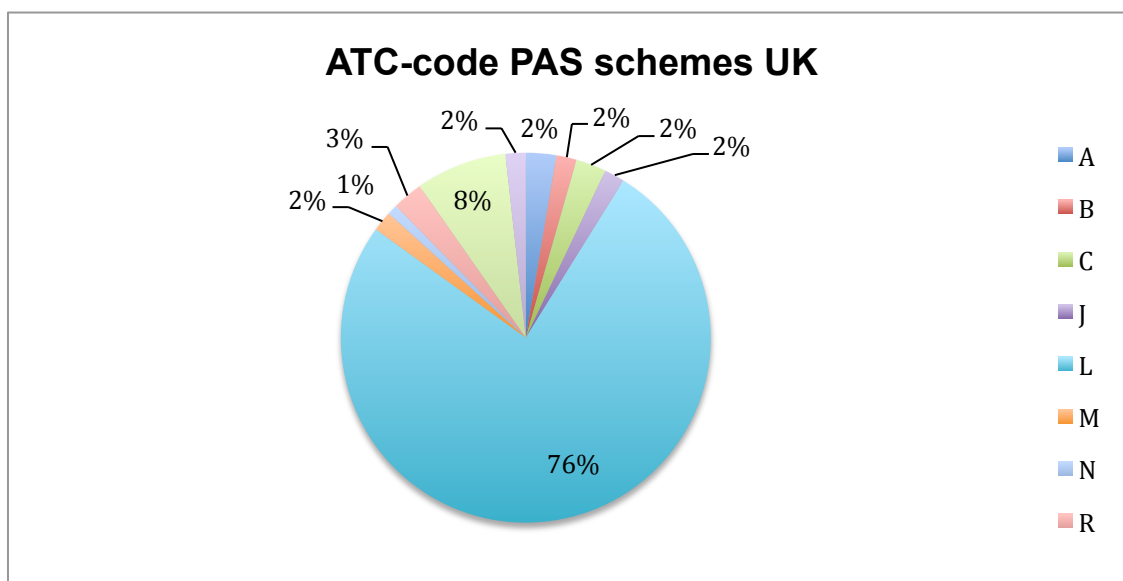


Figure 5. Therapeutic Focus of PAS schemes in England, own presentation based on List of Technologies with approved Patient Access Schemes provided by NICE.

MEAs are heterogeneous applied between the Netherlands and England. Both countries implement mostly financial agreements. However, the amount of MEAs, type of MEA, and targeted drugs differs significantly between England and the Netherlands. For seven drugs, both in England (total amount: n=51) and the Netherlands (total amount: n=21) an MEA is implemented. In England, these all consist of a simple discount in comparison to one CED scheme in the Netherlands, and six financial arrangements consisting of public price cuts with a confidential discount, a price/volume agreement with appropriate use, and public price cuts.

4.7. Implementation of MEAs

4.7.1. Norway

Discounts initiated in the tendering process occur as a reactive process in the direct negotiation between the pharmaceutical manufacturer, and the procurement organization (LIS). The procurement organization (LIS) provides prices to insert in the STAs carried out by NoMA. When these appear to be not cost-effective within certain willingness to pay limits, discounts can be negotiated in order to improve the ICER for the STA. Negotiated discounts on new innovative medicines are confidential in nature.

Moreover, parties are allowed to enter into payback agreements, in order to support the public funding (Helse- og omsorgsdepartementet, 1992). Despite the mentioning of these

agreements in the law, Lov om legmidler of 1992, §6, clear guidance on the implementation of these agreements identified as an MEA are lacking.

4.7.2. The Netherlands

Qualification for conditional reimbursement is possible through two entranceways (Staal & Schelleman, 2016). Parties can apply through a yearly application round, where companies can deliver an application for an intervention they think is suitable for conditional reimbursement (bottom-up), or a manufacturer can submit an application for conditional reimbursement on request of ZIN, after receiving a negative reimbursement decisions (top-down).

The assessment of an application for conditional reimbursement is based on a standard procedure where ZIN advises the minister of health to consider a certain drug as a potential candidate for conditional reimbursement. After a positive decision, all relevant parties are requested to make arrangements with each other to ensure the feasibility and prosperity. These arrangements are written down in a covenant prior to market entrance of the drug in case. The insured population will only receive the treatment if they participate in the research linked to the conditional admission (Staal & Schelleman, 2016). The research linked to the conditional financing requires separate financing. Guideline is that research is financed by a private party, however; there is a possibility to request a subsidy for the research.

The implementation of financial arrangements is established in a similar way. Arrangements are negotiated by the 'Department Financial Arrangements Medicines' part of the Ministry of Health. Five phases are indicated within the process of designing and implementing a financial arrangement, presented in figure 6. Although all relevant actors are involved in the establishment of a financial arrangement, the direction of an arrangement lies ultimately with the Ministry of Health (Ecorys, 2016).



Figure 6. Implementation process of a financial arrangement, adapted from: (Ecorys, 2016; Ministerie van Volksgezondheid Welzijn en Sport, 2014b).

One of the characteristics of financial arrangements is the confidential nature of the negotiations, and agreements, due to the competitive considerations level (Ministerie van

Volksgezondheid Welzijn en Sport, 2016b). A key feature of such an arrangement is that a manufacturer pays back a certain amount of money over a certain amount of years to the insurers (Ecorys, 2016). The payback is arranged through a third trusted party (TTP), who has no role or interest in the negotiations.

The confidential nature of the financial arrangements limits the evaluation of the impact of the individual arrangements. There are only results of the impact of an MEAs on an aggregate level are available, which cannot be linked directly to the individual MEAs (Ministerie van Volksgezondheid Welzijn en Sport, 2016b). In first results of the pilot indicated that in 2014 a expense reduction of 13,9 million euros was realised as a result of the financial arrangements (Ministerie van Volksgezondheid Welzijn en Sport, 2016b). A decrease of 366.000 euro was realised via a decrease in the public list price. Nevertheless, since the 'savings' cannot be traced back to the singular MEAs, the interpretation of savings has to be taken with caution as the circumstances and conditions of these arrangements are not known.

4.7.3. England

PAS arrangements are established through communication between the NHS, and the manufacturer (Department of Health, 2013). PAS arrangements are in the first place, always proposed by the manufacturer of a pharmaceutical product (Ferrario & Kanavos, 2013). Furthermore, a PAS scheme can be part proposed in a response to a negative draft guidance, or in a response to a negative final decision (NICE, 2013). While the manufacturer proposes a scheme, the NHS functions as the price taker, and decides whether to accept a proposed PAS scheme (Carlson et al., 2014).

A simplified process of implementing a PAS proposal consists of four steps, presented in table 5. Key criteria, which are assessed by the NHS, are based upon the degree of administrative burden and cost-effectiveness. Admitted PAS proposals should be clinically robust, clinically plausible, appropriate, and easily to monitor (Department of Health, 2013). Moreover, they should not impose any additional significant burden on the administrative system of the NHS.

Table 5. Implementation process of a PAS adapted from: (NICE, 2009).

Steps within the implementation process:	
1	Pharmaceutical company submits PAS proposal to the Department of Health
2	The department refers the proposal to the Patient Access Scheme Liaison Unit (PASLU)
3	PASLU assesses the proposal against the PPRS principles and provides advice to the Department of Health
4	NICE decides whether the proposed PAS is part relevant appraisal

With the establishment of the PPRS, the Department of Health pointed out that in general all operational PAS schemes should be transparent in nature. The only exception to this principle includes the condition where the minister has agreed on a secret discount, as a result of the specific request of a scheme member to treat the discount rate as commercial-in-confidence prior to submission of their PAS proposal (Department of Health, 2013; Pauwels et al., 2017). Although the discounts can be confidential in nature, the published ICER used for priority setting does incorporate the given discount (Ferrario & Kanavos, 2015).

The studied countries all include as well a proactive approach as a reactive approach in the establishment of an MEA. Nevertheless, the focus on the different two approaches differs between the countries. Where England focuses on proactive implementation, the establishment of financial arrangements in the Netherlands is a more reactive process. Norway handles a reactive process for implementing flat discounts. All three countries include provisions regarding the confidentiality of agreements.

Chapter 5. Stakeholder Input Analysis

This chapter presents the results gathered from analysing the interviews with different stakeholders. Analysed themes that are presented include uncertainty, experience with previous MEAs, MEAs, their perceived advantages and challenges, implementation of MEAs, risk-sharing, and future perspectives of MEAs.

5.1. Uncertainty

Three types of uncertainties were identified in paragraph 2.3. concerning uncertainty regarding the cost-effectiveness, the budget impact, and the use in real-life. These uncertainties function as possible drivers to employ instruments such as MEAs. The primary focus of uncertainty in the Norwegian pricing system is cost-effectiveness: *“The cost-effectiveness is the most important, because it is not many drugs that have a budget impact that is higher than...”* – INT3. In addition, in order to address uncertainty, cost-effectiveness functions as a priority criteria addressed in the Single Technology (STA) assessment carried out by NoMA: *“I could point out that uncertainty regarding cost-effectiveness or clinical effectiveness is really important because those are two of the three prioritization criteria, while budget impact is not a prioritization criteria”.* – INT1.

Nevertheless, some respondents pointed to the importance of budget impact in some cases. One of the respondents (INT2) working for a pharmaceutical company pointed out: *“They use the cost-effectiveness uncertainty to actually reduce the budget impact. I feel that sometimes they use it as a leverage point for making sure this drug will have a lower budget impact because than you can say you have to reduce the price and it will cost less in either the reimbursement scheme or in the hospital”.* Budget impact is likely to play a role in the funding of hospital medicines as one respondent (INT4) elaborates: *“There is both a huge focus on cost-effectiveness and budget impact, and budget implication specifically when it has to be used at the hospital level, because it is going to affect the budget of the hospitals.*

For both cost-effectiveness and budget impact WTP thresholds are considered, however these are confidential in nature. The thresholds depend on the severity of a specific disease. In 2018, a new document on priority setting in health care will be published, which will address the topic on WTP.

5.2. Managed Entry Agreements

In the current health care system, there are two kinds of agreement implemented. First, it is pointed out that under the working definition presented in the theoretical framework, MEAs are applied in the form of flat discounts. Discounts are part of a combined process of assessing and pricing drugs. When NoMA finds a new drug not to be cost-effective, with the provided price from LIS, this will likely result in a negative reimbursement decision. As a result, LIS and the pharmaceutical company might go into new price negotiations possibly resulting in a lower price, which in turn will cause an ICER to be cost-effective. Second, one respondent (INT3) pointed out that after the law in 2016 had changed to allow payback schemes, several payback schemes have been implemented since. *“So we have a sort of pay-back system for these new products for cholesterol, a product for individual reimbursement. And we have one agreement in our system for hospitals, and they say at the top never again, because that deal is not good.”* Nevertheless, the conditions of these agreements are not public due to the confidential nature of the agreements. Despite discounts, limited experiences using MEAs have occurred in the past, although a couple of MEAs have been applied *“Before my time working here we had an MEA scheme for a product, I think that was a volume-based contract, where the company was supposed to pay back a certain amount or percentage of overuse by some criteria”* – INT2.

5.3. Strengths and Challenges of MEAs

Different strengths and challenges were indicated. Strengths and challenges can be divided according to general observations, and specific perceptions related to financial arrangements or outcome-based arrangements. In general, MEAs are perceived as a possibly helpful instrument in the process of improving access to patients: *“That is a strength about these agreements; it is possible to get access to get more products.”* – INT3. MEAs could provide the possibility to make drugs available if the normal instruments are lacking to do so.

Financial agreements provide the opportunity for authorities to easily target uncertainties regarding the cost-effectiveness of a drug. Furthermore, financial agreements are overall perceived as easy to implement, and administer. The strengths were illustrated by mentioning the discount system. Nevertheless, one respondent (INT4) pointed to challenge that financial agreements could easily be used to only put down the costs, while the price does not reflect the appropriate value of the drug anymore.

One of the perceived strengths of outcome-based agreements includes the support for value-based agreements, as it is agreed to be best to measure outcomes. However, it is argued

that this is only the case if it is easy to measure. Moreover, opportunities to collect better evidence are created *“The strength is that you take risk of for the government, and you make it easier for the business to prove the effect.”* – INT5. Nevertheless, it has to be noted that not all respondents had sufficient answer on the strengths, as there is a lack of experience. Respondents on both the supplier as purchaser side agreed on several challenges. For both parties the main challenge perceived towards agreements that are more complex are the practicalities of the implementation of these agreements. A main practicality includes the administrative burden it might impose, and difficulties related to monitoring, and performance: *“We most agree on that it is appropriate to measure outcomes, but then doing it and agreeing what outcome to measure and the time-horizon is very resource demanding and complex intellectually.”* – INT2. Another respondent (INT4) elaborates on this by indicating that there is a lot of data fragmentation within the health care system, in addition to lacking infrastructure to measure these outcomes within hospitals. It is even mentioned that doctors are not allowed to take upon more responsibilities regarding measuring outcomes. Furthermore, one of the participants (INT2) also stretched the desirability of the agreements: *“If you shape them theoretically well, they might be extremely difficult to follow-up on, and that’s then you have to weight what are the benefits of doing it.”* This points towards the value of information on implementing different agreements to assess whether these are socially desirable.

5.4. Implementation

There is coherence among stakeholders that the use of MEAs should function as an additional instrument to the existing system for pricing, and reimbursement. When the normal instruments fail to provide sufficient access, MEAs could be utilised instead: *“From a resource point of view it will be natural to do it after you see the ordinary root does not take us where we want to go.”* – INT2. An MEA could be proposed if noticed that another way is needed than the usual pathway. The option should be integrated to the existing pricing system, where an agreement has to be presented to NoMA and LIS, as LIS has to provide prices to NoMA, which can be used in the STA to calculate the ICER of a drug.

Two processes of establishing MEAs are indicated. The implementation of discounts is a reactive process as a discount can be proposed after a negative recommendation from NoMA: *“I can inform the company and LIS that this will be probably be negative unless you come up with a rebate.”* – INT1. In contrast, implementing more complex agreements is likely to be a mix of a reactive and proactive approach as pharmaceutical companies are encouraged to propose new innovative solutions: *“We are asking the companies to give us*

suggestions and we get new suggestions every month, and then we will see if we want to tell the managing director at the top that we want to try a new system because they have to approve it.” – INT3.

Several features have been pointed out on the sufficient implementation of MEAs within the theoretical framework, paragraph 2.5. Before implementing an MEA, it is important that all stakeholders agree on which conditions are important to use specific agreements. One important condition mentioned by a respondent (*INT4*), is the clarity on the desirability of agreements: *“It is important to have flexibility of course, and clarity about why the agreement is necessary in that situations, and under which circumstances might this scheme apply.”* If all stakeholder parties engaged in the establishment of an agreement, understand the arrangements, than everyone can benefit mutually as a result: *“If the agreements are good, and everyone understand what they entail, and what the consequences are I think it could benefit everyone” –INT1.* When a lack of clarity on the desirability of an agreement and its consequences occurs, a case of asymmetrical information is likely to rise, as the respondent (*INT1*) elaborates: *“Once you introduce a special kind of agreement that has a level of complexity that makes on of the parties not fully understand what the consequences are, then it is just benefiting the party that knows all about it.”* Further conditions to achieve clarity of an agreement include clarity on the measurement of a component, and who should take responsibility for what.

The subject of transparency raised different discussion points from the respondents. One respondent pointed out that open access would be of significant importance to support best practice across European countries. Nevertheless, this is not feasible if agreements are confidential in nature, due to a lack of comparability. In contrast, one respondent addressed the issue of competitive considerations in the context of external reference pricing: *“We cannot have open prices and expect to have low prices in a small market as Norway, because the Germans, the French, and the English they will say: well you can give this price in Norway, we should have the same price here, and we’ll have extreme losses.” – INT5.*

5.5. Risk-Sharing

Different perspectives were retrieved on risk sharing between the different parties. Core to this discussion is the risk adverse nature of the purchaser, in this case the government. The two experts representing the pharmaceutical industry pointed towards the risk aversion of the authorities against new opportunities: *“They are very risk averse, meaning that you know*

they lose a lot of opportunities, in my opinion on this, which I think is very unfortunate.” – INT2.

In contrast, it was pointed out that it is some willingness to have some risk on the authorities, however, they need to have security on what variables to put in the STA: *Most risk for an agreement should be on the industry, because they are presenting the data.” – INT3.* One respondent elaborated that the risk should be evaluated in every single case: *“If this is something you really want as an agency, you want to bear higher costs or risk. And if you as a company, your big block-buster like to be introduced because then you can get all kind of sorts of introduction to the market and will help entail you in the development of new indications for example, than I think they should bear a higher risk.” – INT1.* One option, which was suggested by different participants, included reflecting the risk in the price, through collecting more effectiveness data and adjusting the price to the level of evidence.

5.6. Future perspective

Respondents recognised that new methods of pricing and reimbursement or arrangements are necessary to ensure sustainable access to new drugs: *“We see that in the future we need to have more types of agreements than we have today.” – INT3.* Several perspectives of how this should be entailed in the future were given in the interviews. One of the aspects mentioned included the development of value-based pricing and health care. *“With many stakeholders in health care is the key for a more sustainable health care future in Europe – INT4.* The respondent argued that if MEAs have to be placed in a framework, it is important to connect MEAs to value-based health care, as the agreements could function as a mean to improve the development of value-based health care. Another respondent (*INT1*) points out that a logical first step into this direction would be the implementation of indication specific pricing: *“Once you do value-based pricing, it does not make sense to not have indication specific prices”* as the value for different indications can heavily vary. In addition, the change in the law is mentioned, which allows engaging in a payback agreement: *“That gives a signal that it may be possible to make new type of agreements.”*

Nevertheless, due to the lack of good examples, the different stakeholders treat the subject of MEAs with caution. One respondent (*INT3*) pointed out that: *“We see that in the future we need to have more types of agreements than we have today. But we don’t know which type of agreements.”* Purchasers want the new drugs, however, they want to purchase the drugs at an affordable price, to prevent wasting public resources. Therefore, it is pointed out that to

further develop the discussion on MEAs: *“You really need to identify specific success factors, so legal factors, regulatory factors, and health policy factors for good agreements.”* – INT4.

Chapter 6. Discussion

The discussion presents the findings of the country comparisons and interviews, interpreted in the light of the theoretical framework analysed according to the different sub-questions presented in paragraph 1.1. Paragraph 6.1. shortly points out the main findings of the study, whereas paragraph 6.3. discusses the different findings in depth.

6.1. In what way are arrangements, related to uncertainty, conducted for the introduction of new pharmaceutical products organized in different countries?

To the knowledge of the author, this is the first study, to include Norway within the cross-country comparison of MEA utilization. First, within all three studied countries at least one form of MEA is introduced, however all are utilised under different terminology. Second, a clear tendency towards financial arrangements is evident in both England and the Netherlands. Norway shows the same tendency with the implementation of discounts; however, more research is needed on the total amount of implemented MEAs, and respectively their different types. Third, previous research indicated that MEAs were relatively most often applied in disease areas with therapeutic focus ATC-L (Ferrario & Kanavos, 2015; Morel et al., 2013). This is endorsed by later studies conducted in the specific area of oncology (Pauwels et al., 2017; van de Vooren et al., 2015). The conducted study showed that to different extents, this disease focus was still the largest group targeted in both the Netherlands and England. Only a limited amount of medicines had an application of an MEA in both the Netherlands and England. Fourth, implementation processes are established in different manners, involving proactive, reactive, or the use of both approaches. Lastly, all three countries have included provisions in their policies or legal acts concerning MEAs, constituting the confidential nature financial details might take.

6.2. What are different rationales for the use of MEAs?

Similar reasons are cited for applying MEAs in all three countries. MEAs are utilised in order to manage uncertainties about the budget impact, cost-effectiveness, and/or use in real-life (Klemp et al., 2011). Improved access to medicines is mentioned as an overall target, with different ways of achieving this. The framework developed by Ferrario & Kanavos (2015), presented in figure 1, paragraph 2.3., highlighted differences across implementation within the three different countries. The Netherlands was the only country to highlight budget impact in their policy documents regarding financial arrangements. In contrast to England and Norway, who solely mention cost-effectiveness as a policy objective, while avoiding the concept of budget impact. By means of the framework, however, it can be argued that

budget-impact is indirectly targeted through the utilization of simple discounts in both countries. Therefore, the two main rationales to implement an MEA include concerns about the budget impact, and cost-effectiveness. Nevertheless, confidentiality in prices can complicate the process to review and standardise the rationales for setting up MEAs (Morel et al., 2013).

6.3. What causes the variation in MEA and non-MEA use (Norway) between different countries?

The previous findings lead to the discussion why significant differences and trends occur within the application of MEAs. Several factors might contribute to a certain extent to the variation in MEA utilization. First, the lack of consistency in used terms for MEAs across countries leads to different views. Although the concept of an MEA is not used as such everywhere, similar instruments are likely to be in place. The identification of MEAs is challenged by different terms, and perspectives to what constitutes an MEA across countries (Ferrario & Kanavos, 2015). The case of Norway shows while literature indicated that MEAs were currently not utilised, simple discounts are common practice within the purchasing process. Due to the lack of terminology, different forms of policies, and different legislative acts, a certain notion should be taken regarding the comparability of MEA application across countries (Pauwels et al., 2017).

Second, several reasons might explain the clear trend in the use of financial arrangements. There might be an increasing emphasis on the importance of containing budget impact instead of targeting underlying uncertainties about the clinical- and/or cost-effectiveness. Such a development is not surprising as health policy makers seek greater certainty on overall expenditures (Kanavos et al., 2017). Financial arrangements make it easier to control this aspect. Furthermore, poor experiences with measurement and data gathering will obtain payer parties from engaging in outcome-based agreements. Over the last years ZIN experienced that data gathering only poorly addressed the uncertainties left at the initial conditional reimbursement decision (Pauwels et al., 2017). The implemented CED schemes helped gathering information about costs and appropriate use of drugs, however, showed only limited value for clinical effectiveness development (Gerken et al., 2017). The development of clinical data was however, one of the rationales for implementing CED schemes in the Netherlands. Nevertheless, a study by Toumi, Jarosławski, Toyohiro, & Kornfeld (2017) showed that CED schemes can provide value in the uncertainty regarding clinical effectiveness. Although, contextual differences with regards to infrastructure to collect data, and the supply chain of speciality affects the feasibility to apply certain types of MEAs

in certain countries (Pauwels et al., 2017). The cost of data collection and administration is often higher than the value additional information provides (Edlin et al., 2014). This challenge supports advocating the utilization of VOI analysis within HTA procedures. A VOI analysis is of significant importance to assess whether an (outcome-based) agreement is desirable (Garrison et al., 2013). Moreover, analysing the cost of additional might become more urgent, as a greater number of submissions is expected with a evidence base that is smaller or earlier in its development (Grimm et al., 2016). Whether a specific scheme is desirable is considered a pre-contractual problem, VOI analysis could increasingly contribute to overcome this problem.

Moreover, it is suggested that the link between different WTP, and the choice for MEA implementation should be explored (Ferrario & Kanavos, 2015). This is the first study regarding MEAs to incorporate a WTP for the Netherlands. In England, a significant lower maximum WTP threshold is being utilised than in the Netherlands. In addition, the amount of financial agreements in the form of simple discounts differs significantly compared to the amount of agreements incorporating a discount in the Netherlands. The lower WTP threshold is one likely way to explain the high amount of financial agreements, and especially the simple discounts applied in England. Nevertheless, more cases should be studied in depth to verify this association, although it might be challenging studying the effect of WTP due to confidentiality in financial details. In addition, some countries have no publicly published WTP thresholds, such as the case in Norway, which often results of political pressures. This in turn, will restrict the comparison across countries.

The third finding showed a relative similarity in targeting of disease areas. The finding, however, might divert in the future as a result of the limited amount of financial arrangements (19) that have been implemented in the Netherlands. Nevertheless, treatments with a focus in disease are ATC-L are expected to maintain a promising area for MEAs, due to the rapid dynamics in the oncology market (Pauwels et al., 2017). Only a limited amount of medicines showed an MEA application in both the Netherlands and England. There is no clear explanation for this variation. Ferrario & Kanavos (2015) pointed out that other instruments might be available to facilitate access, such as the utilization of end-of-life criteria and the cancer drug fund. Nevertheless, both instruments cannot explain the significant higher number of schemes in England compared to the Netherlands. Moreover, there are indications that the WTP for end-of-life criteria only have a maximum threshold of 50.000 pounds (Stewart et al., 2014), however more research is needed to verify this. Nevertheless, this gives an indication that as well for the application of MEAs, WTP function as a significant

driver. It has to be noted though that more similarities would have been likely to occur if more countries were included in the country comparison.

The fourth finding showed heterogeneous implementation processes. Kanavos, Ferrario, Tafuri, & Siviero (2017) argued that the specifications of contracts and implementation conditions vary according to context. Legislative and policy frameworks explain some of the differentiation within MEA implementation. Moreover, there are certain variances in the proactive or reactive approaches to establish an MEA, although the involvement of all parties in the agreements seems to be of importance. The proactive manner utilised in England, is likely due to the fact that WTP thresholds are well-known in England, which results in more manufacturers proposing the agreements prior to the application process (Ferrario & Kanavos, 2015).

The last finding showed that confidentiality protection is one of the foundations of MEA utilization (Pauwels et al., 2017). Confidentiality results from competitive considerations towards other pharmaceutical companies. Moreover, MEAs allow pharmaceutical companies to influence the reference price in a confidential manner, which in turn affects the price within other countries (Leopold et al., 2012). The lack of transparency within the agreements, however, result in several challenges. In the first place it challenges studying the effects MEAs have on variables such as the budget impact. Furthermore, the lack of transparency complicates the comparison of agreements across countries. The lack of transparency also points towards the challenges in external reference pricing utilised in a significant amount of countries (Pauwels et al., 2017).

6.4. How do Norwegian stakeholders value MEAs?

The presented findings of the interviews were reliant on the opinions of different stakeholders. Due to the lack of real-world evidence on the implementation of MEAs, described strengths and challenges were perceived from past experiences and/or theoretical considerations. Strengths and challenges, were therefore similar to the ones cited in literature, such as presented in table 2, chapter 2. MEAs are considered as a promising instrument to ensure access to patients. Stakeholders recognised the need for an additional range of instruments in order to target uncertainties within the reimbursement process. Nevertheless, a lack of good examples in literature and real-life, especially considering more complex agreements, prevents these agreements from being utilised yet.

Viable through the interviews was the perceived agency problem involved with MEAs, from a purchasers perspective. Payer parties emphasised that a certain security within the assessment of data is necessary to evaluate medicine as eligible for reimbursement. To overcome this pre-contractual problem before the design of agreements, clarity on the agreements, and social desirability of an agreement in terms of opportunity costs, is of significant importance to supplier, and purchasers parties. The interviews showed that the VOI is important to overcome issues in pre-contractual problems. Therefore, besides the common perceived impracticalities of MEAs, two concerns arised; the lack of knowledge on 'appropriate agreements', and difficulties in advance of establishing MEAs.

6.5. What are the lessons, Norway could learn from international experiences?

The on-going utilization of MEAs across countries underlines the significance of these instruments as a satisfying conduct for numerous policy imperatives, while risk is mitigated (Kanavos et al., 2017). Moreover, the use of MEAs points to issues and limitations related to the use of current approaches of reimbursement and HTA methods in addressing uncertainties and determining reasonable prices (Kanavos et al., 2017). Nevertheless, MEAs should not be used as an easy instrument to neglect usual pricing and reimbursement, or cost containment systems and policies (Gerkens et al., 2017). However, due to the pressure on authorities to regulate timely access to innovative drugs, and cost containments, MEAs are likely to be further developed in the future.

To utilise MEAs in appropriate ways, the instruments should be an integrated part of the process of managed introduction of new pharmaceutical products (Kanavos et al., 2017). Alignment with horizon scanning, HTA practices, and pricing and reimbursement systems should be considered. Heterogeneous practices of reimbursement systems across countries will make the choice of an MEA context dependent. Nevertheless, if agreements are well designed and used in accordance, payer parties should be enabled to optimize recommendation regarding new, and existing technologies in a predictable, transparent and rational manner (Grimm et al., 2016). Assessing the value of information will be a way to assess the risk of implementing an MEA. The sustainability of MEAs will rely on the ability of parties to design an arrangement that is mutually beneficial in entailing administrative burden in development and implementation (Carlson et al., 2014).

Nevertheless, there is a scope for further research. In the first place, the studied impact of MEAs is still scarce these days (Ferrario & Kanavos, 2015; Gerkens et al., 2017). More

research is needed on the question whether MEAs fulfil the objectives for which they are implemented. Evidence on the impact of MEAs in turn, will result in more appropriate guidelines on the utilization of MEAs, which will support the development of good practice. Furthermore, the influence of WTP on the number of MEAs, and choice for MEA design should be further researched.

6.6. Limitations

In addition to methodological limitations, presented in paragraph 3.7, the study included several research limitations, which might indicate prospects for future research. First, the literature review regarding European experiences explaining the variations in MEA utilization was not systematic in nature. However, it is believed that through pearl growing, all key studies and articles have been identified.

Second, the study included a limited sample size, both within the country comparison as the interviews. There is a need to analyse different characteristics and effects, in order to exchange best practice between countries and stimulate policy learning. The stakeholder section included interviews with only five participants. This however, is not considered to be a large issue, as the interviews were used as a case study to get an indication what is going on in the Norwegian stakeholder landscape, and explorative in nature. Time related choices had to be made on the inclusion of countries, and participants.

Furthermore, some aspects have not been discussed in depth for Norway, since there was only limited information available on the practice of MEAs. Further research might provide more information on the practice of MEAs within Norway. Language limitations might have contributed to this limitation. As the researcher is not fluent in Norwegian, this might have resulted in missing certain policy documents or important information.

6.7. Conclusion

The analysis highlighted different developments and patterns in the utilization of MEAs across Norway, the Netherlands, and England. Several variables contribute to explain trends and variations occurring across countries, such as the relative growing importance of budget impact, and the differences in utilised WTP. Nevertheless, further research scopes were identified to support the appropriate use of MEAs. Furthermore, the research explored the attitude towards MEAs among Norwegian stakeholders, which pointed to the necessity of more research towards good examples due to the insecurities about the impact of the agreements.

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APPENDIX 1. MEA Taxonomies

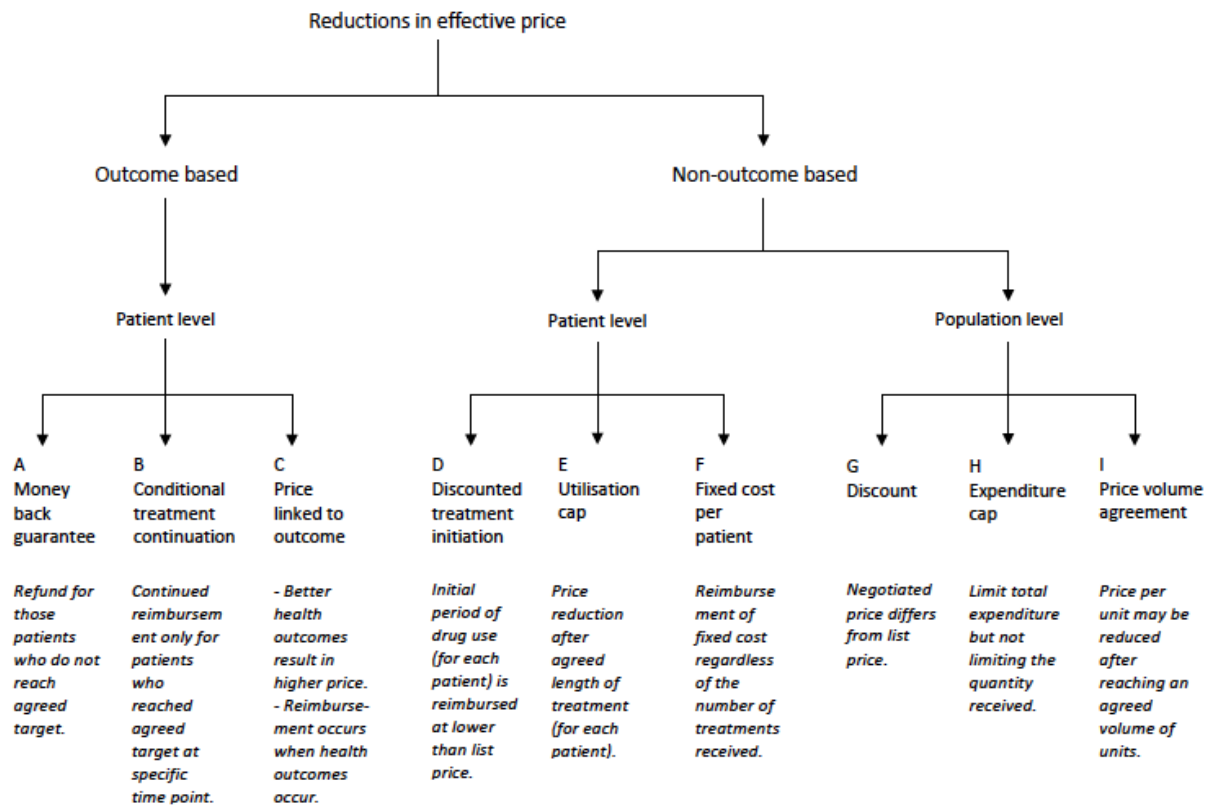


Figure 7: MEA options (Retrieved from Grimm et al., 2016).

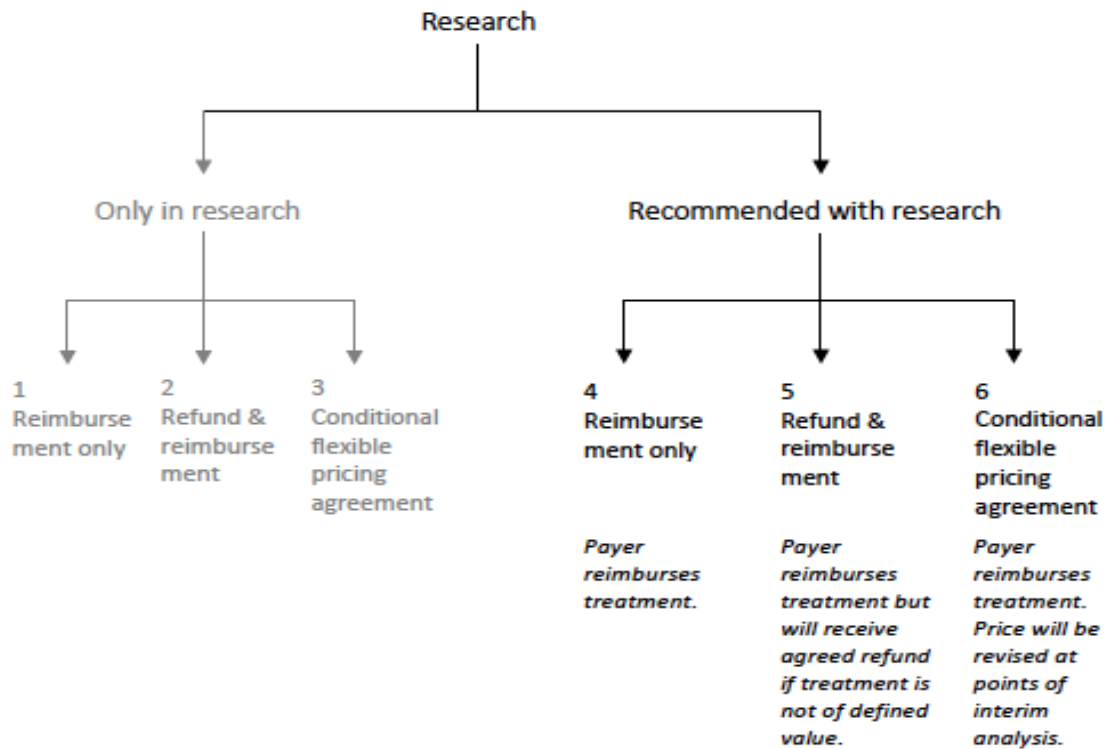


Figure 8: MEA options (Retrieved from Grimm et al., 2016).

Appendix 2. References studying the impact of MEAs

Table 6. List of references studying the impact of MEAs.

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APPENDIX 3. Research Philosophies

Four types of philosophies are distinguished in literature including pragmatism, positivism, realism, and interpretivism (Saunders et al., 2009; Thomas, 2004). Table 7 gives a short, but clear introduction of the different philosophies.

A *Pragmatism Philosophy* recognizes that one single perspective is not able to give the overview, therefore multiple realities might exist (Saunders et al., 2009). There are different perspectives of interpreting real-world data, and undertaking a research. A *Positivism Philosophy* only accepts the quantifiable knowledge received through measurement and objective observation (Saunders et al., 2009). In this perspective a researcher only functions for the data collection, and interpretation. A *Realism Philosophy* states that the reality is independent from the human mind. This approach is divided in two subgroups; *direct realism* (“what you see is what you get” (Saunders et al., 2009)), and *critical realism*: (what humans experience and perceive of the real world, can be subjective, and not how the real world is portrayed (Novikov & Novikov, 2013)). According to an *Interpretivism Philosophy* access to reality takes place through the development of social constructions, such as language, consciousness, and shared meaning (Myers, 2008).

Table 7: Key Characteristics different Research Philosophies

	Pragmatism	Positivism	Realism	Interpretivism
Research Approach	Deductive/Inductive	Deductive	Deductive/Inductive	Inductive
Research Strategy	Both Qualitative and/or Quantitative	Quantitative	Both Qualitative and/or Quantitative	Qualitative
Popular methods for data collection	Mixed design or multiple different methods. Can be Qualitative and Quantitative in nature.	Based on measurement Large samples Highly structured	Methods chosen must fit the subject matter quantitative or qualitative	Qualitative research design. Small samples In depth research

APPENDIX 4. Consent Form

I have read the information presented in the information letter about a study being conducted by Marjolein Peters of the Institute of Health and Society at the University of Oslo. I have had the opportunity to ask any questions related to this study, to receive satisfactory answers to my questions, and any additional details I wanted.

I am aware that I have the option of allowing my interview to be tape recorded to ensure an accurate recording of my responses.

I am also aware that excerpts from the interview may be included in the dissertation and/or publications to come from this research, with the understanding that the quotations will be anonymous.

I was informed that I may withdraw my consent at any time without consequences by informing the researcher.

With full knowledge of all foregoing, I agree, of my own free will, to participate in this study.

YES NO

I agree to have my interview recorded on tape.

YES NO

I agree to the use of anonymous quotations in the thesis that comes of the retrieved data.

YES NO

Participant's Name: _____

Participant's Signature: _____

Date:

Researcher's Name:

Researcher's Signature: _____

Date:

APPENDIX 5. Interview Protocol

A: Introduction (Not recorded):

- Introduction of the interviewer
- Introduction of the research
- Introduction of the interviewee
- Introduce why the person was involved
- Introduce and discuss consent form, and if necessary any ambiguities

B: Uncertainty:

- In what way does Norway cope with the introduction of high-cost drugs?
- Which type of uncertainty is addressed in general policy?
- How is dealt with uncertainty regarding budget impact and cost-effectiveness?

C: MEAs:

The concept of Managed Entry Agreements (MEAs) might be a new concept, as currently these agreements are not used in Norway. MEAs contain an arrangement between a [pharmaceutical] manufacturer and a payer/provider that enables access to a health technology subject to specific conditions. The arrangements can use a variety of mechanisms to address uncertainty about performance of medicines or to manage the adoption of medicines in order to maximize their effective use, or limit budget impact.

- Is/Has there been any experience in the past with MEAs?
- Considering the definition of MEAs is there any experience with mechanisms such as price discounts etc.?
- Based on what you know of MEAs, what would be your opinion about MEAs:
 - o Strengths?
 - o Weaknesses?
 - o Opportunities
 - o Threats?

D: Introduction of MEAs:

- Would MEAs fit into the Norwegian reimbursement system, and where?
- What would you like to see in the implementation of such a process?

E: Stakeholder collaboration:

- Is there a long-term relationship between different stakeholder parties? In what way do you work together?
- Do you think MEAs could offer mutual benefits to all involved parties including pharmaceutical manufacturer, payer and patient?

- In such an agreement how should risks be shared between different parties?
- How should and is currently monitoring and performance included?

E: General questions:

- Do you think difficulties in introduction uncertainty ask for different methods than the established methods?
- Do you think tightening health care budgets ask for different methods than the established methods?
- Do you think MEAs could represent a way forward for introducing expensive innovative drugs?
- If not, do you think other improvements could be made in the current pricing and reimbursement system?

F: Closing of the interview:

- Ask if the respondent has anything to add to the interview.
- Thank the respondent for his/her collaboration.
- Ask whether the respondent would like to see a transcript of the interview.

APPENDIX 6. Approval of Research



Oddvar Martin Kaarbo
Institutt for helse og samfunn Universitetet i Oslo
Postboks 1130 Blindern
0318 OSLO

Vår dato: 10.05.2017

Vår ref: 53999 / 3 / AMS

Deres dato:

Deres ref:

TILBAKEMELDING PÅ MELDING OM BEHANDLING AV PERSONOPPLYSNINGER

Vi viser til melding om behandling av personopplysninger, mottatt 05.04.2017. Meldingen gjelder prosjektet:

<i>53999</i>	<i>Managed Entry Agreements as a strategy for introducing new high cost medicine</i>
<i>Behandlingsansvarlig</i>	<i>Universitetet i Oslo, ved institusjonens øverste leder</i>
<i>Daglig ansvarlig</i>	<i>Oddvar Martin Kaarbo</i>
<i>Student</i>	<i>Marjolein Peters</i>

Personvernombudet har vurdert prosjektet og finner at behandlingen av personopplysninger er meldepliktig i henhold til personopplysningsloven § 31. Behandlingen tilfredsstiller kravene i personopplysningsloven.

Personvernombudets vurdering forutsetter at prosjektet gjennomføres i tråd med opplysningene gitt i meldeskjemaet, korrespondanse med ombudet, ombudets kommentarer samt personopplysningsloven og helseregisterloven med forskrifter. Behandlingen av personopplysninger kan settes i gang.

Det gjøres oppmerksom på at det skal gis ny melding dersom behandlingen endres i forhold til de opplysninger som ligger til grunn for personvernombudets vurdering. Endringsmeldinger gis via et eget skjema, http://www.nsd.uib.no/personvernombud/meld_prosjekt/meld_endringer.html. Det skal også gis melding etter tre år dersom prosjektet fortsatt pågår. Meldinger skal skje skriftlig til ombudet.

Personvernombudet har lagt ut opplysninger om prosjektet i en offentlig database, <http://pvo.nsd.no/prosjekt>.

Personvernombudet vil ved prosjektets avslutning, 30.11.2017, rette en henvendelse angående status for behandlingen av personopplysninger.

Vennlig hilsen

Kjersti Haugstvedt

Anne-Mette Somby

Kontaktperson: Anne-Mette Somby tlf: 55 58 24 10

Dokumentet er elektronisk produsert og godkjent ved NSD's rutiner for elektronisk godkjenning.



The sample will receive written information about the project, and give their consent to participate. The letter of information is well formulated.

The Data Protection Official presupposes that the researcher follows internal routines of Universitetet i Oslo regarding data security. If personal data is to be stored on portable storage devices, the information should be adequately encrypted.

Estimated end date of the project is 30.11.2017. According to the notification form all collected data will be made anonymous by this date.

Making the data anonymous entails processing it in such a way that no individuals can be recognised. This is done by:

- deleting all direct personal data (such as names/lists of reference numbers)
- deleting/rewriting indirectly identifiable data (i.e. an identifying combination of background variables, such as residence/work place, age and gender)

LAST PAGE