Access to orphan drugs in Norway

An explorative study of the market access landscape for orphan drugs in Norway

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Abstract

Introduction and theory: The US and EU developed special legislation to promote the development of drugs for patients with rare diseases (orphan drugs). *Rare diseases* are defined as <5 patients out of 10,000 inhabitants. The priority criteria consist of; health-benefit, resource, and health loss. With the System for Managed Introduction of New Methods in Norway operationalising the priority criteria, there has been increasing debate on orphan drugs and New Methods extensive focus on price. With new pharmaceuticals required to undergo Health Technology Assessment, decision-makers expect orphan drugs to satisfy their willingness-to-pay threshold. However, there are no policies for the rapid implementation of orphan drugs in Norway.

Methods: Quantitative methods were applied; we developed descriptive statistics and used the Mann-Whitney U-test, a two-sample test of proportion and logistic regression analysis.

Results: 67 of 132 orphan drugs are accessible in Norway. Adoption of orphan drugs takes more than two years on average from Market Authorisation is granted by EMA. There is a significant disease burden for rare diseases in Norway; the burden is more significant for non-cancer patients than cancer patients. Patients with rare diseases could benefit significantly from the pharmaceuticals considered by New Methods, with a mean gain of 2 QALYs. The odds of reimbursement increase with the increasing disease burden, while increasing costs decrease the odds. The number of positive decisions on orphan drugs has decreased following the White paper on priority setting. NoMA and manufacturers evaluate the effect of new orphan drugs significantly different.

Discussion: Patients with rare diseases in Norway are heavily burdened by their condition. The long period between a medication receiving marketing authorisation and a decision adds to the patient's burden and counteracts EU Regulations designed to promote rapid access to orphan drugs. Many orphan drugs are for cancer conditions; the current legislation might facilitate a lucrative drug area such as cancer. Several orphan drugs would qualify for New Methods' higher willingness to pay, except that they are too many patients. And New Methods might put too much weight on the priority criteria, neglecting other important factors.

Conclusion: We recommend looking to other countries to improve the reimbursement process in Norway to rapidly adopt new pharmaceuticals and increase the legitimacy of the process. Observing the debate on rare cancer drugs within orphan drugs, we recommend that EU design two separate Marketing Authorisation tracks to provide them with appropriate incentives, respectively.

Acknowledgements

I would like to extend my gratitude to my supervisor Ivar S. Kristiansen for his extensive patience with me during this though period. Also, to my friends and colleagues, I want to thank you for all support and interesting discussions. And to Asle, who supported me and allowed me to work all to many hours on my thesis, I thank you dearly.

Conflict of interest: The original dataset was given to me by my employer, Rud Pedersen.

Table of content

Tables

Introduction

The Regulation on Orphan Drugs was passed in the EU in 1999 (REGULATION (EC) No 141/2000, 2000), incentivising manufacturers of pharmaceuticals to develop medicines for patients with rare diseases. Preceding the enactment of the Orphan Drug Act in the United States of America and the EU Regulation, patients with rare diseases, had little or no access to pharmaceutical treatment (Swann, 2018). While regulatory frameworks are in place to facilitate rapid Marketing Authorisation, most European countries, including Norway, do not have policies or legal frameworks to enable fast access to orphan drugs (Sarnola *et al.*, 2018). The Norwegian healthcare system has undergone several changes since 2000. Recent changes in the financial responsibility for orphan drugs have made the situation between patients, medicine manufacturers, and the system tenser. Decades of public debate on priority setting and orphan drugs led to the Parliament requesting an evaluation of the System for the Managed Introduction of New Methods (New Methods), which was finalised in autumn 2021. As part of addressing the critique raised against New Methods, the Government are preparing a new White Paper on priority setting in healthcare which is expected in autumn 2023. While the debate has spurred on the access situation of orphan drugs in Norway, little research has been done on the subject.

This thesis will explore the access to orphan drugs in Norway.

In the next chapter, we will build a theoretical foundation. The processes will be described, and terms and events will be defined. Finally, we will provide some theories on economics, ethics and what is known on the subject. A brief discussion of the theory culminates in the research question and hypothesis.

Chapter 3 describes the methods used to collect data material and its processing to develop descriptive statistics and hypotheses tests. The chapter continues by describing logistic regression analysis and the development of the model.

Chapter 4 starts with descriptive statistics before the results of the tests described in chapter 3 are presented.

Finally, chapter 5 summarises the main results. We briefly discuss our findings and address the strengths and weaknesses of our research. A short comparison is made to findings in other studies before policy recommendations, and a conclusion is provided.

Theory

Development of pharmaceuticals

Pharmaceuticals are developed for treating diseases by private pharmaceutical companies, although public-owned pharmaceutical companies exist (FDA, 2018a). It is a complex and capital-intensive process which takes ten years from discovery to it can be prescribed to patients. Pharmaceutical companies aim to maximise profit, maximising return to investors and shareholders. The development of pharmaceuticals consists of five phases:

- Discovery
- Preclinical research
- Clinical research
- Review by a regulatory body and Marketing Authorisation
- Post-Market Authorisation safety monitoring

To make discoveries and advances in pharmaceutical therapy, companies are dependent on unique insight into the disease process, a large number of tests to find beneficial effects, examining unanticipated effects of existing treatments, and new technological advances (i.e. CRISPR). Potential compounds are reduced from 5,000-10,000 in the discovery phase to one granted marketing authorisation; the process is often called "the valley of death" (Zurdo, 2013). Clinical research consists of four phases of clinical trials to evaluate the safety and efficacy of the drug (**Error! Reference source not found.**).

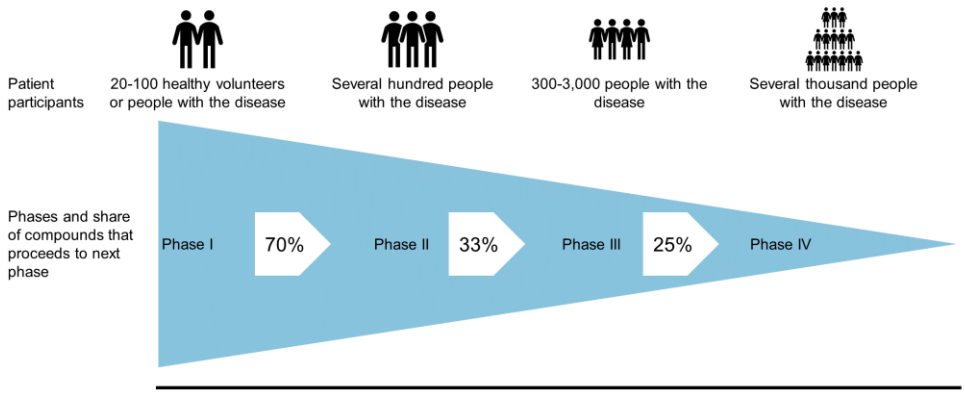


Figure 1 phases of clinical trials (FDA, 2018b)

Taking this long and complex process into account and the high risk of failing to get a compound to the market, pharmaceutical companies reduce their risk by allocating resources and capital to compounds with a high potential of making it to the market, covering a large patient population to achieve the best return on their investments (Bagley *et al.*, 2019).

Legislators acknowledged that smaller patient populations suffered from the risk-averse behaviour of pharmaceutical companies. The market mechanisms led to small patient populations being neglected and unable to access efficient treatment for their disease or condition. To correct an imperfect market, legislators designed a regulatory framework to promote the development of pharmaceuticals for small patient populations with rare diseases.

Rare disease

The term "rare disease" is arbitrary, and its definition varies by country and region. Richter et al. (2015) found that quantitative thresholds and qualitative descriptions define rare diseases. The most common quantitative threshold to define rare diseases was ≤40 patients per 100,000 inhabitants. Through time, the definition of rare disease has changed several times in Norway, from a qualitative description, to a quantitative definition of ≤100 patients per 1,000,000 inhabitants (NOU 1997:7, 1997) to the definition today of ≤5 patients per 10,000 inhabitants (Helse- og omsorgsdepartementet, 2021). While there is a definition of rare diseases and a strategy for rare diseases, rare diseases have no material or processual rights in Norway.

Regulatory framework on orphan drugs

The United States of America (US) was the first to pass an act providing pharmaceutical companies with incentives to develop pharmaceuticals for patients with rare diseases in 1983(Orphan Drug Act, 1982). While several countries have developed a regulatory framework to promote the research and development of orphan drugs, most countries have no special legislation to encourage the development of orphan drugs (Bagley *et al.*, 2019). This subsection will explore the orphan drug act in the US and the European Union (EU) Regulation on orphan drugs.

US Orphan Drug Act

Five thousand different rare diseases and conditions affected 20-25 million Americans, who faced a massive burden of disease and little or no treatment options in the 1980s. Following pressure from patient organisations representing non-cancer conditions, Congress intervened (Orphan Drug Act, 1983; 1982; Bagley *et al.*, 2019; Swann, 2018). Setting a threshold of ≤200,000 patients to qualify, Congress provided three measures aimed at encouraging pharmaceutical companies to increase effort in researching and developing pharmaceuticals for patients with rare diseases:

- Seven years of market exclusivity
- Tax credits
- Research grants

Acknowledging the financial risk for companies developing orphan drugs and the risk of competition from "me-too drugs" (medications similar to, with equivalent effect and for the same condition as the first-in-class pharmaceutical (Aronson and Green, 2020)) and generics, Congress provided seven years of market exclusivity, a form of supplementary protection certificate to existing patents. Additionally, Congress relieved the economic burden of companies developing orphan drugs by providing them with 25% tax credits for qualified clinical trials (50% until 2017) and grants and contracts for a cumulative sum of USD 30 million. The Orphan Drug Act has contributed to a rise in the development of Orphan Drugs, from 10 orphan drug Approvals in 1983 to 77 Orphan Drug Approvals in 2017. 50% of orphan drugs authorised between 1983 and 2014 were first-in-class (Karst, 2018; Miller and Lanthier, 2016). While non-orphan drugs need evidence equivalent to a phase III clinical trial, the Orphan Drug Act exempts orphan drugs from this level of evidence, acknowledging both the difficulties in performing such trials and the urgency of getting efficient treatment to patients with rare diseases (Orphan Drug Act, 1983; 1982).

European regulation on Orphan Drug

Facing the same challenges as the US did in the 1980s, the EU passed special regulations on orphan drugs in 1999. As with the Orphan Drug Act, REGULATION (EC) No 141/2000 (2000) provides several incentives for the pharmaceutical industry to develop and bring orphan drugs to the European market:

- Ten years of market exclusivity
- Reduction of fees related to Marketing Authorisation procedures
- Protocol assistance in the form of scientific advice
- Access to centralised authorisation procedures
- Administrative and procedural assistance from EMA for small and medium-sized enterprises

Contrary to the US, which defined a rare disease as ≤200,000 patients, the Regulation defines a rare disease with a prevalence of ≤5 per 10,000 inhabitants, making it a total of 30 million Europeans with a rare disease when the European Parliament and European Council enacted the Regulation.

Since the introduction of the Regulation, the European Commission has granted 2,382 Orphan Designations by 2020, of which 190 have resulted in authorised medicinal products(European Medicines Agency, 2021). Although the EU developed special legislation to encourage pharmaceutical companies to develop orphan drugs, most countries, including Norway, have not followed up with policies or legislation to promote the utilisation of orphan drugs.

Norwegian Health Care System and Governance

Norway has a universal, nationalised healthcare system. The counties governed hospitals until 2002. Following a blame game between counties and the Government on consistent overspending of budget, the Government nationalised hospitals through trusts and set hard budget constraints to stop deficits (Hagen and Kaarbøe, 2006). Being semi-decentralised, the central Government is responsible for specialised healthcare through four Regional Health Authorities (RHA) which own 20 hospital trusts (Figure 2) (Saunes, Karanikolos and Sagan, 2020). Three hundred fifty-six municipalities are responsible for primary healthcare, and 11 counties are responsible for dental care. Reimbursement of prescription pharmaceuticals follows the institution responsible for initiating, assessing, and stopping treatment. The Directorate of Health decides who carries the financial responsibility for medications of RHA and the National Insurance Scheme. The individual RHA is responsible for financing pharmaceuticals, delegated through budgets to the respective clinic at each hospital. For medicines prescribed in primary healthcare and dental care, the National Insurance Scheme carries financial responsibility. Provided the National Health Insurance Scheme are responsible for reimbursement of the drug, it undergoes a Health Technology Assessment (HTA) by the

Norwegian Medicinal Agency (NoMA). If NoMA finds the pharmaceutical fulfils the priority criteria set by Parliament (see the section below), and the budget impact is less than NOK 100 million, NoMA can grant reimbursement. The Ministry for Health and Care Services takes over case processing if the expected budget impact of adopting the pharmaceutical exceeds NOK 100 million. The Ministry of Health and Care Services proposes budgetary adjustments for Parliament. If the RHA is responsible for reimbursement, the RHA has developed a system to assess and adopt new pharmaceuticals (see subsection Following the Norwegian Official Report by the Norheim Commission and the subsequent report by the Magnussen group, the Government submitted a White Paper on Priority Setting to Parliament in 2016. In line with the recommendations from the Norheim Commission and the Magnussen group, the White Paper stated three priority criteria; health benefit, resource, and health loss as measured as an absolute shortfall (St. meld 34 (2015-2016), 2016). The White Paper discussed rare diseases as a possible criterion but did not find convincing reasons to include it, stating it would undercut the other criteria and establish a precedent for other Patient advocacy groups. The System for Managed Introduction of New Methods founded by RHA operationalised the criteria.

System for managed introduction of New Methods in specialised health care in Norway).

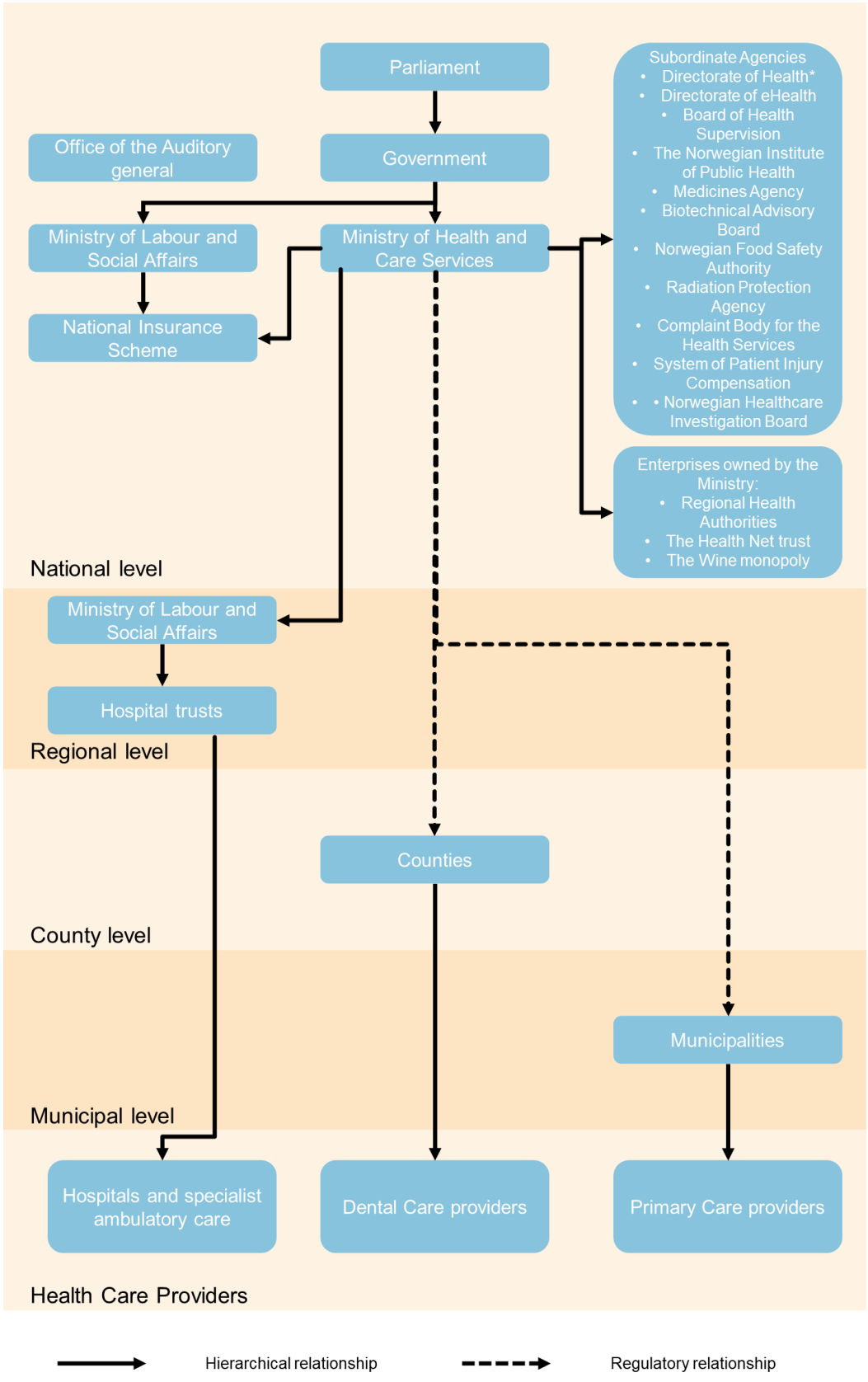


Figure 2 Overview of the Norwegian Healthcare system (Saunes, Karanikolos and Sagan, 2020)

Norwegian Official Reports on Priority Setting

Norway experienced a rapid expansion of the healthcare system and increased spending on healthcare following 1950 and onwards with the discovery of petroleum in the North Sea in the 1970s (Saunes, Karanikolos and Sagan, 2020). Realising that the galloping spending on healthcare could not continue on constrained budgets, the Government initiated the first Norwegian Official Report on priority setting in healthcare in 1987 (Lønning I Commission) (NOU 1987:23, 1987). Lønning I Commission set forward five levels of priority. A decade later, in 1997, the Government commissioned a new Official Report on priority setting (Lønning II Commission), which set forward four levels of priority, stating the goal for the healthcare sector to be "more good life years for all" (NOU 1997:18, 1997). Lønning II touched upon rare diseases, stating that treatment abroad for patients with rare diseases and conditions or complex conditions was justifiable if patients did not have access to clinical expertise in Norway.

The Norheim Commission submitted the latest Norwegian Official Report in 2014. It stated that the goal of the Norwegian health system is to achieve *"as many good life years as possible for all, distributed fairly"* (NOU 2014:12, 2014). The Norheim Commission concluded to ensure the desired balance between equity and efficiency, with three overarching criteria; health benefit, resource, and health loss. Quality Adjusted Life Years (QALYs) would measure Health benefit criteria by combining health-related quality of life and survivability gained by the intervention (pharmaceutical). The amount of resources required (in monetary terms) to implement the intervention represents the resource criterion. Finally, the health-loss criterion was the total amount of QALYs lost over a standardised lifespan of 80 years. Norheim suggested expressing resources and health-benefit as a fraction (Incremental Coste-Efficiency Ratio (ICER). However, the Norheim Commission considered that the ICER should be supplementary, taking other non-quantifiable considerations of equal importance. The health-loss criterion received critiques in a public hearing on the report. As the Ministry of Health and Care Services were unsatisfied with it, it commissioned a new report on the health-loss criterion, appointing the Magnussen group to give its views in a report. The Magnussen group recommended using "absolute shortfall" as the health-loss criterion (Magnussen *et al.*, 2015a). Absolute shortfall describes the future QALYs lost due to the disease for a person relative to the life expectancy in Norway. We will use the more general term "burden of disease" in later sections. In line with the Norheim Commission, the Magnussen group recommended a

weighted relationship between the severity of health loss, calculated from the absolute shortfall approach, and a WTP threshold.

Table 1 Relationship between QALYs lost and WTP (in thousands NOK) per QALY (Magnussen *et al.*, 2015b)

Group	**1**	**2**	**3**	**4**	**5**	**6**
QALYs lost	0-3.9	4-7.9	8-11.9	12-15.9	16-19.9	20+
Weight	1	1.4	1.8	2.2	2.6	3
Upper limit per QALY	275	385	495	605	715	925

White Paper on Priority Setting

Following the Norwegian Official Report by the Norheim Commission and the subsequent report by the Magnussen group, the Government submitted a White Paper on Priority Setting to Parliament in 2016. In line with the recommendations from the Norheim Commission and the Magnussen group, the White Paper stated three priority criteria; health benefit, resource, and health loss as measured as an absolute shortfall (St. meld 34 (2015-2016), 2016). The White Paper discussed rare diseases as a possible criterion but did not find convincing reasons to include it, stating it would undercut the other criteria and establish a precedent for other Patient advocacy groups. The System for Managed Introduction of New Methods founded by RHA operationalised the criteria.

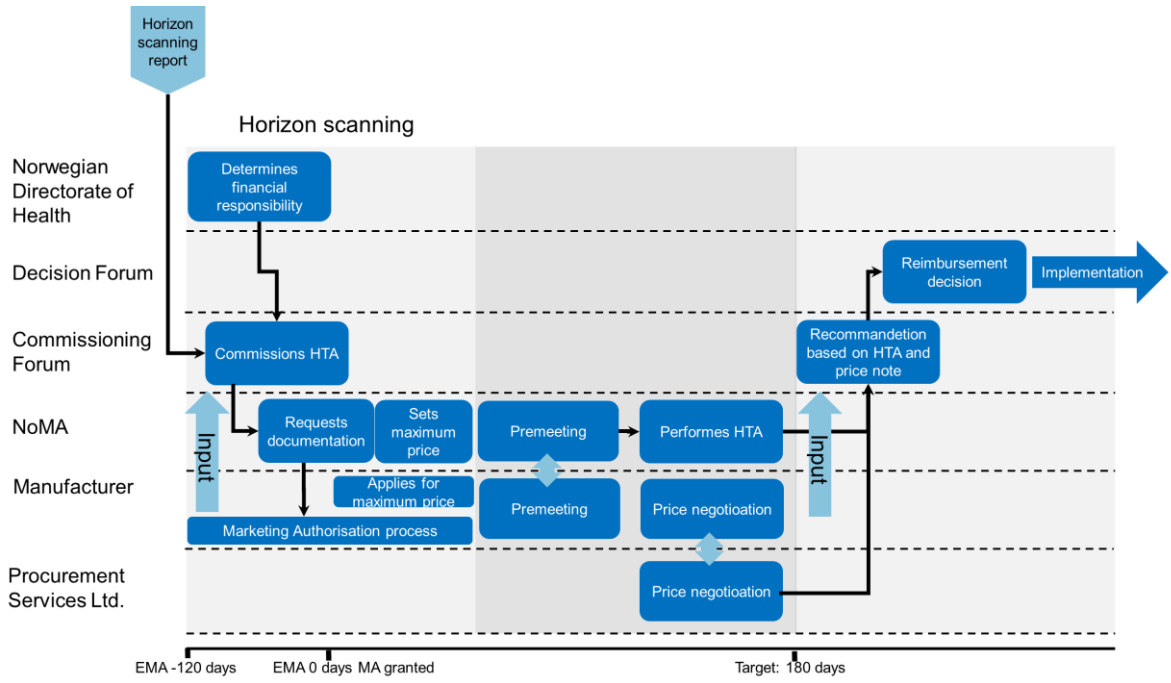
System for managed introduction of New Methods in specialised health care in Norway

HSRs are generally written six months before Marketing Authorisation (MA) following a pipeline meeting between manufacturers, NIPH and NoMA (Figure 3). Manufacturers can submit input to the report before submission and further processing. Commissioning Forum commissions either a full Health Technology Assessment performed by NIPH or a single Health Technology Assessment (HTA) performed by NoMA. We will explore the latter in this paper. Following the commissioning of an HTA, NoMA requests the submission of documentation from the manufacturer.

Upon MA, manufacturers apply for a maximum price to NoMA. NoMA decides on a price through a reference price system, using the three lowest prices from a selection of 9 European

countries. After the manufacturer submits documentation to NoMA, NoMA arranges a premeeting with the manufacturer, and NoMA subsequently initiates the HTA report. The Procurement services for Health Enterprises Ltd. initiates price negotiation with the manufacturer. The Procurement services submit a price note to NoMA or Commissioning Forum, depending on the time of finalising price negotiations. Upon completing the HTA, manufacturers can provide input to the HTA before submission to Commissioning Forum, which gives its recommendation to Decision Forum. Decision Forum decides on reimbursement, keeping priority criteria in view, based upon the recommendation, HTA, price note and collected input from health care professionals. (For full details on the system is provided in Appendix 1).

Figure 3 process of reimbursement in Norway (Nye Metoder, 2022; 2021a)



Ethics

Utilitarianism aims to achieve the highest attainable level of utility or happiness for everyone (Universitetet i Oslo Institutt for filosofi, 2015). In the healthcare sector, we can define utilitarianism as attaining the highest possible level of good health and longevity. Cost-effectiveness analysis can be one application of utilitarianism, distributing justice and maximising overall health to bring the highest health outcome to the greatest number of people (Olsen, 2009). While utilitarianism aims to achieve the most increased health for as many

people as possible, Rawls considers it differently. Rawls argues that if all were under a veil of ignorance and nobody knew their role and place in the social hierarchy before removing the veil, they would choose to maximise the primary good to benefit those worst off. According to Rawls, inequalities in society can exist as long as they benefit those who are the worst off. Rawls's theory of justice can be reflected in health care by the person most disadvantaged, prioritising patients with the most immediate threat of death.

Economic theory

Economic theory states that resources are scarce, and one must prioritise; giving up one thing is called *opportunity cost (Krugman and Wells, 2008).* In health economics, when considering a new pharmaceutical, the treatment displaced or not adopted are the opportunity cost.

Economic theory strives toward a perfect market (Krugman and Wells, 2008). A perfect market must meet four assumptions; consumers and sellers taking the market price for granted; homogenous goods; complete information; and no transactional costs. An imperfect market occurs when there is a violation of the assumptions of a perfect market. In a competitive market, the price and quantity are a function of demand and supply (Figure 4 Supply and demand curve in a competitive market (Krugman and Wells, 2008)

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Figure 5Figure 6 Supply and demand curve in a competitive market (Krugman and Wells, 2008)

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Figure 7 Supply- and demand curve in a monopolistic- and monopoly market with average cost curve (Krugman and Wells, 2008)

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Figure 8Figure 9Figure 10 Supply curve in a competitive market and Wells, 2008)

Figure 8Figure 9Figure 10 Supply and demand curve in a competitive market (Krugman and Wells, 2008)

and demand (Krugman

Figure 11Figure 12 Supply and demand curve in a competitive market (Krugman and Wells, 2008)

Figure 11Figure 12). If production increases, the marginal cost curve shifts right, lowering the price (P*) and increasing quantity (Q*). If consumption increases, Marginal willingness to pay changes right, increasing both price (P*) and quantity (Q*).

In an imperfect market, such as a monopolistic market, these functions do not hold. The pharmaceutical market is

Figure 13 Supply- and demand curve in a monopolistic- and monopoly market with average cost curve (Krugman and Wells, 2008)

Figure 14Figure 15 Supply- and demand curve in a monopolistic- and monopoly market with average cost curve (Krugman and Wells, 2008)

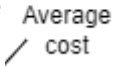


Figure 16 Data material

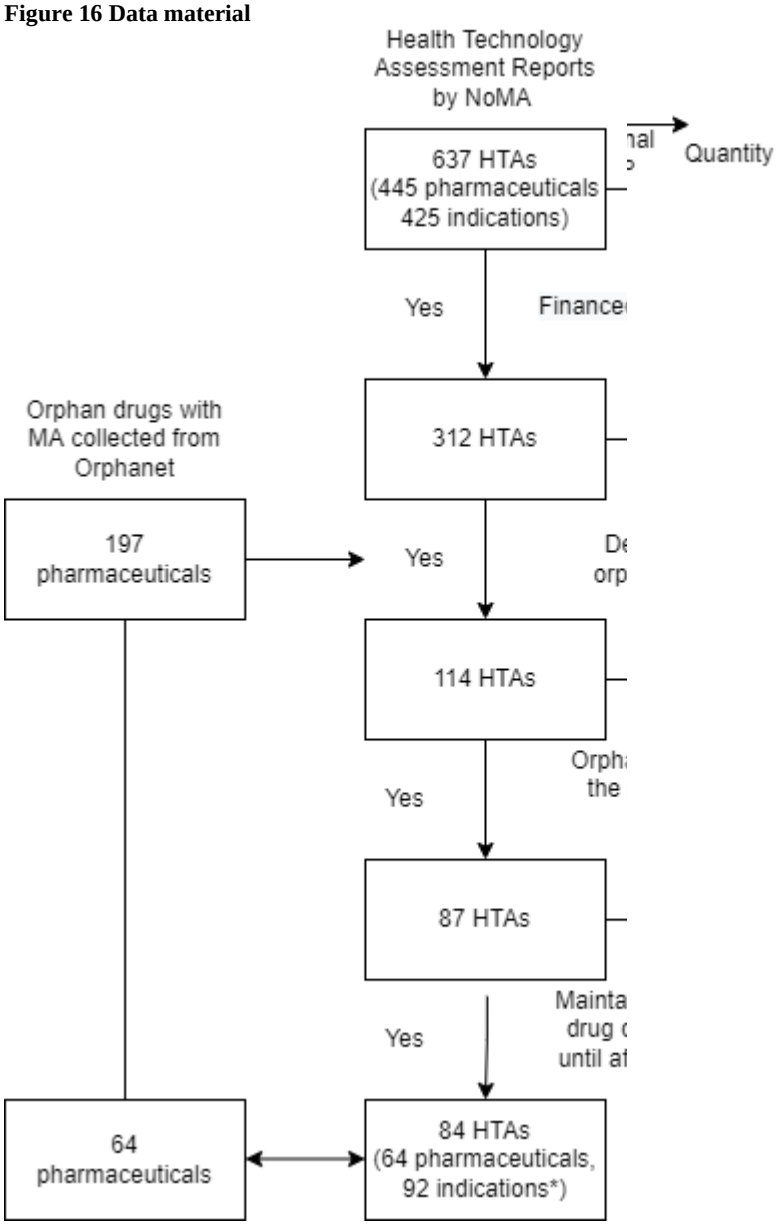


Figure 17Figure 18 Supply- and demand curve in a monopolistic- and monopoly market with average cost curve (Krugman and Wells, 2008)

Figure 19Figure 20 Supply- and demand curve in a

monopolistic, and the manufacturer sets the price equal to the lowest willingness to pay at the given quantity (Figure 13 Supply- and demand curve in a monopolistic- and monopoly market with average cost curve (Krugman and Wells, 2008)

Figure 14Figure 15 Supply- and demand curve in a monopolistic- and monopoly market with average cost curve (Krugman and Wells, 2008)

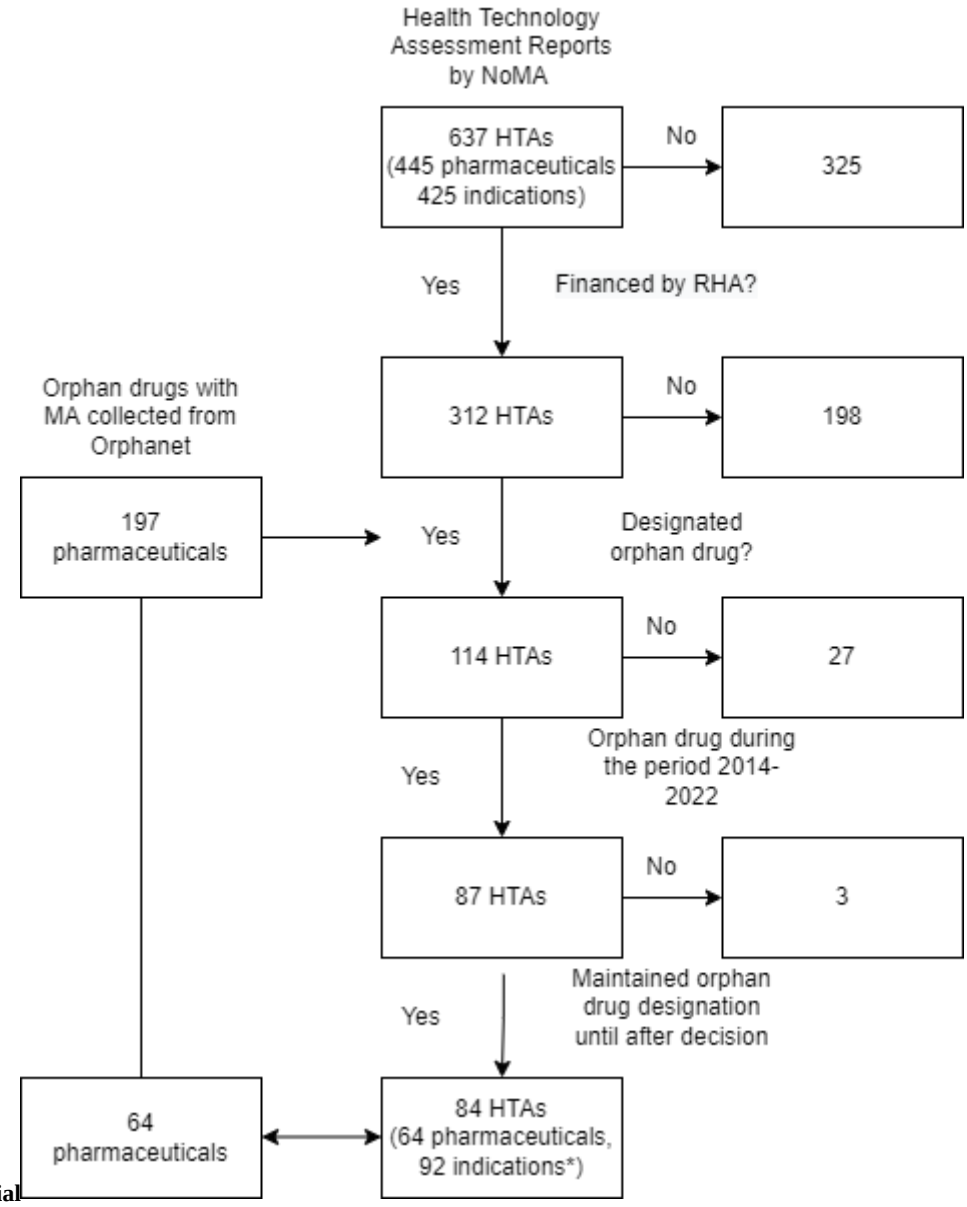


Figure 16 Data material

Figure 17Figure 18 Supply- and demand curve in a monopolistic- and monopoly market with average cost curve (Krugman and Wells, 2008)

Figure 19Figure 20). To achieve the highest degree of profits, manufacturers set the quantity (QM) provided equally where the marginal cost curve intersects with the marginal revenue (the marginal revenue curve drops at twice the rate of the marginal WTP curve).

Economic evaluation

In financially constrained healthcare systems such as Norway, there is an increasing focus on demonstrating that healthcare interventions are cost-effective (Briggs, Claxton and Sculpher, 2006). Economic evaluation requires all appropriate evidence to be incorporated into the analysis and compare the intervention with alternative options. The economic evaluation aims to quantify the costs and benefits of an intervention. Additionally, it can inform decision-makers on the uncertainty of evidence and provide large probabilistic and deterministic models to assist decision-makers. An economic evaluation's main result of interest is the Incremental Cost-Efficiency Ratio (ICER). To calculate the ICER, the incremental costs are divided by the incremental effect (QALYs gained). Several interventions can be compared in the same analysis, allowing the decision-maker to rank the ICERs and pick intervention(s) until the budget is exhausted. However, when NoMA performs HTAs with economic evaluation, only one comparator is used, the standard of care at the time of evaluating an intervention.

Individual reimbursement and transferral of financial responsibility

Pharmaceuticals for treating rare conditions and diseases were reimbursed on individual application (individual reimbursement) to the national insurance administration from 1960 (NOU 1997:7, 1997). The National Insurance Scheme granted individual reimbursement for pharmaceuticals intended to treat rare conditions and diseases without considering the severity of illness, cost-efficiency and lower burden of evidence on the efficiency (St. meld 34 (2015-2016), 2016). Case reports were considered sufficient evidence for patient populations smaller than 30 until changes in Regulation in 2018 (St. meld 34 (2015-2016), 2016; Ministry of Health and Care Services, 2017). Following the White paper on priority setting, the Norwegian Directorate of Health transferred financial responsibility for 62 orphan drugs for treating rare conditions and diseases from the National Health Insurance Scheme to Regional Health Authorities in 2019 (Ministry of Health and Care Services, 2017; Norwegian Directorate of

Health, 2019). The Norwegian Directorate of Health transferred the remaining orphan drugs and pharmaceuticals intended to treat rare conditions and diseases from the National Insurance Scheme to Regional Health Authorities in 2021(Norwegian Directorate of Health, 2020).

Public debate on New Methods and access to orphan drugs

Public discussion of priority setting and pharmaceutical access has consisted over the last decades. Patient organisations for rare diseases filed a lawsuit against Government, demanding access to pharmaceuticals (later withdrawn) (Bordvik, 2019). Before transferral of financial responsibility, patients and manufacturers cried out about the danger of a more challenging access environment for patients with rare diseases. Some have criticised cancer drugs for taking the focus from the original intention of the legal framework, making the lucrative cancer drug market more lucrative by the incentives provided by the legal framework (Miller and Lanthier, 2016; Seachrist, 1993; Côté and Keating, 2012). Patients and manufacturers criticised New Methods for lacking transparency, being slow-moving, rigorous and making it "all about the money" (Hanssen and Nilstad, 2021) . Following the intervention of the former Minister of Health and Care Services to reimburse the pharmaceutical Yervoy in 2013, politicians have since been reluctant to overrule decisions by New Method (Storvik, 2014). The integrity of New Methods was utterly cemented by the amendment to the Specialist Healthcare Act in 2019, enacting New Methods. However, during Parliamentary proceedings, Parliament instructed Government to evaluate the system New Methods.

Evaluation of New Methods

Autumn 2021, Proba Samfunnsanalyse handed over their report to the Minister of Health and Care Services on New Methods. The report finds broad support for the underlying principles of New Methods and the rationale for priority setting (Proba samfunnsanalyse, 2021). They found strong support for the scientific approach of evaluating evidence produced through clinical trials and health economic evaluation. However, there are reasons to question whether New Methods's design and operation are optimal for rapidly adopting new health technology. Compared to England, Sweden, Denmark and Scotland, Norway is adopting new pharmaceuticals at a lower rate than the three first countries, sharing ranks with Scotland.

The report pointed out six challenges for the system (Proba samfunnsanalyse, 2021):

- The goals set for the system are widespread and not in line with the resources available.

- Lack of trust exists between internal actors and external stakeholders, which goes both ways.
- Somewhat slower and weaker access to treatments compared to countries we compare ourselves with.
- Lack of guidelines to ensure equal implementation and use of new methods.
- The New Methods System does not work as intended concerning the evaluation and implementation of MedTech.
- Future therapies will challenge the current system, and it won't be easy to ensure good processes for these treatments under the current framework.

Previous research

While the number of studies in this area is limited, Sarnola *et al.* (2018) found that Norway had adopted 7 out of 10 recently approved orphan drugs, compared to the mean of 5 out of 10. Further, most countries, such as Norway, did not have policies or regulations for assessing or pricing orphan drugs. Newton, Scott and Troein (2022) found that 21 of 57 orphan drugs Authorised in the period 2017-2020 were available for patients in Norway, in line with the mean availability in Europe. In terms of time to availability, measured from the date of marketing authorisation to the date of reimbursement decision, Norway had a mean time of 583 days. In relative terms, 37% of approved orphan drugs were publicly available, 33% privately available (out-of-pocket), and 30% were unavailable. Gustafsson and Limseth (2021) in a survey for LMI (Pharmaceutical Industry Association), the least available medicinal products were orphan drugs in the period 2015-2019. They also observed a low degree of utilisation of orphan drugs in Norway, finding that only cancer had lower utilisation than orphan drugs. Nilsen (2021) examined reimbursement decisions and the utilisation of cancer drugs and drugs for multiple sclerosis. There was an increase in number of positive reimbursement decisions for all drugs. Though New methods reimbursed several drugs during 2014-2020, some drugs were never used. Nilsen concluded that New Methods operationalises the priority criteria. Moss (2021) investigated the QALYs gained by new pharmaceuticals in Norway in the period 2014-2020, and found a significant difference in the estimates used by manufacturers and NoMA.

Gaps in knowledge

Based on the theory chapter, there is a considerable gap in knowledge. There is much information about the Norwegian healthcare system, drug approval and reimbursement processes. However, there is limited knowledge on market access in general and in Norway, the expected benefit of orphan drugs, and the burden of rare diseases.

Research question and hypothesis

The development of drugs takes several years before it is available to patients. However, the regulatory framework has been designed to reduce the burden of evidence needed and speed up the process of providing pharmaceuticals to people with rare diseases suffering from a significant disease burden. While no framework is provided to shorten the reimbursement process in Norway, we do not know the time it takes for orphan drugs to be reimbursed. The New Methods system was designed to adopt new technology rapidly; according to Proba, it does not manage this to keep up with comparable countries.

The priority criteria state that decision-makers should increase their willingness to pay with the growing burden of disease, which was to be operationalised through New Methods. Yet, little is known about how New Methods apply the priority criteria.

Based on the theory in this chapter, this master thesis aims to address the following research questions:

- Which drugs given EMA orphan drug designation during 2014-2021 have been used by Norwegian patients, and for what diseases?
- Which orphan drugs were used according to the individual reimbursement rules?
- Which orphan drugs have been evaluated by Nye metoder, what was the main conclusion of the evaluation, and have they been approved for use by the Decision Forum?
- What are the main characteristics with rare diseases?

Based on the research questions, this master thesis aims to test the following hypothesis:

1. Willingness-to-pay for orphan drugs based on maximum approved price is increasing with increasing absolute shortfall.

2. Positive reimbursement decisions for orphan drugs have increased following the white paper on prioritisation in 2016.
3. Costs of treatment and effectiveness of orphan drugs measured in quality adjusted life years gained with orphan drugs are estimated differently by NOMA and the manufacturer.
4. There has been no change in access to orphan drugs previously reimbursed under the National Health Insurance Scheme following its transfer to Regional Health Authorities 1. February 2019.
5. No orphan drugs are reimbursed without price negotiation before the decision in Decision Forum.
6. Orphan drug designation for medicinal products for cancer treatment has increased d 2014-2021.

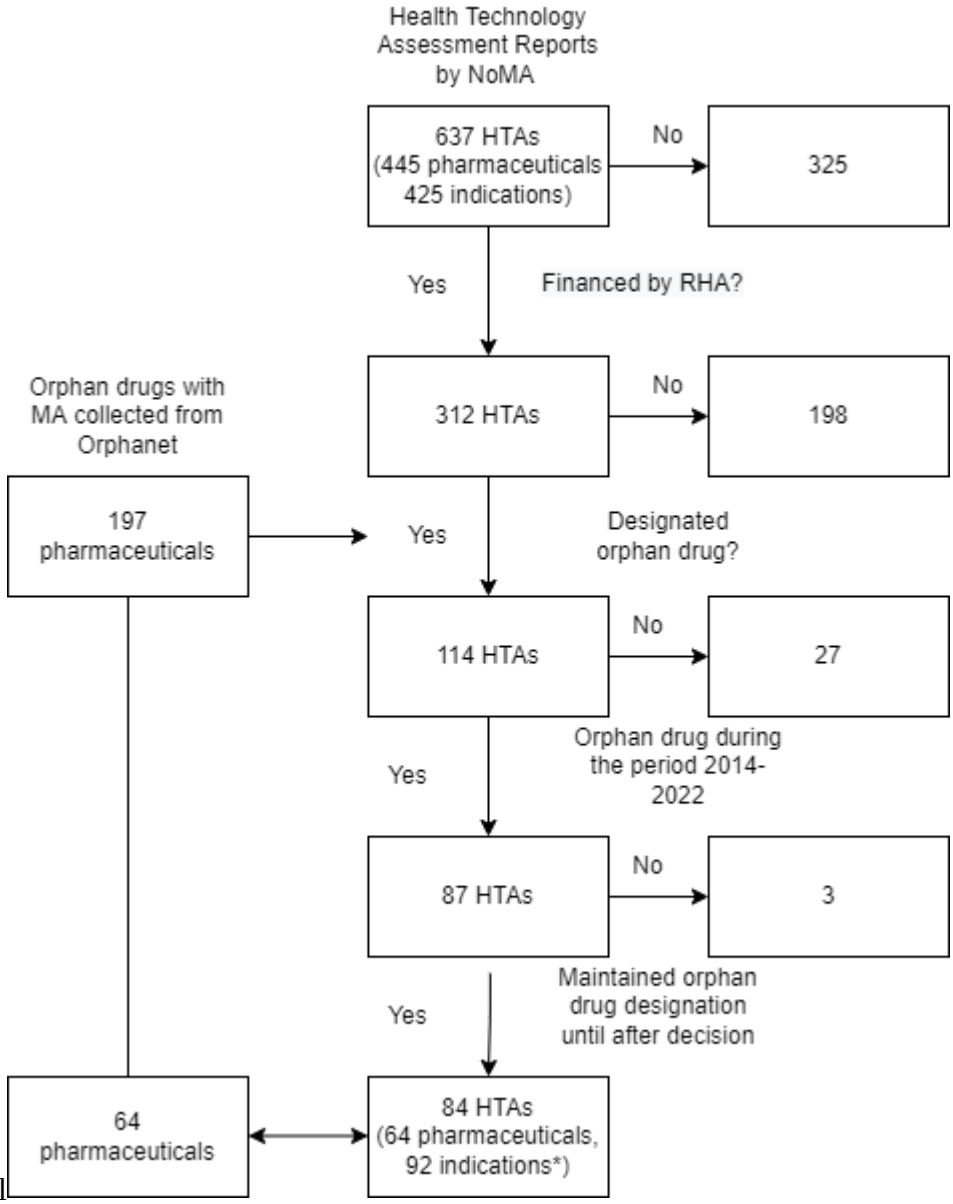
Research methods

Based on the theory section, research question and hypothesis above, we aim to investigate access to orphan drugs in the period 2014-2021 by using a quantitative approach.

We considered quantitative methods to be the best approach as “hard” data forming the basis of decisions and decisions made by the Decision Forum. Quantitative data allows exploration of willingness to pay for orphan drugs, the costs associated with adoption of orphan drugs, health effect and burden of disease among others. As the data sample were small, we applied a significance level of 10% and confidence intervals of 90% if not mentioned otherwise.

Material

Based on a report issued by Orphanet (Lists of medicinal products for rare diseases in Europe, 2021) we collected data on all orphan drugs authorised by the European Commission (Figure 21 Data material



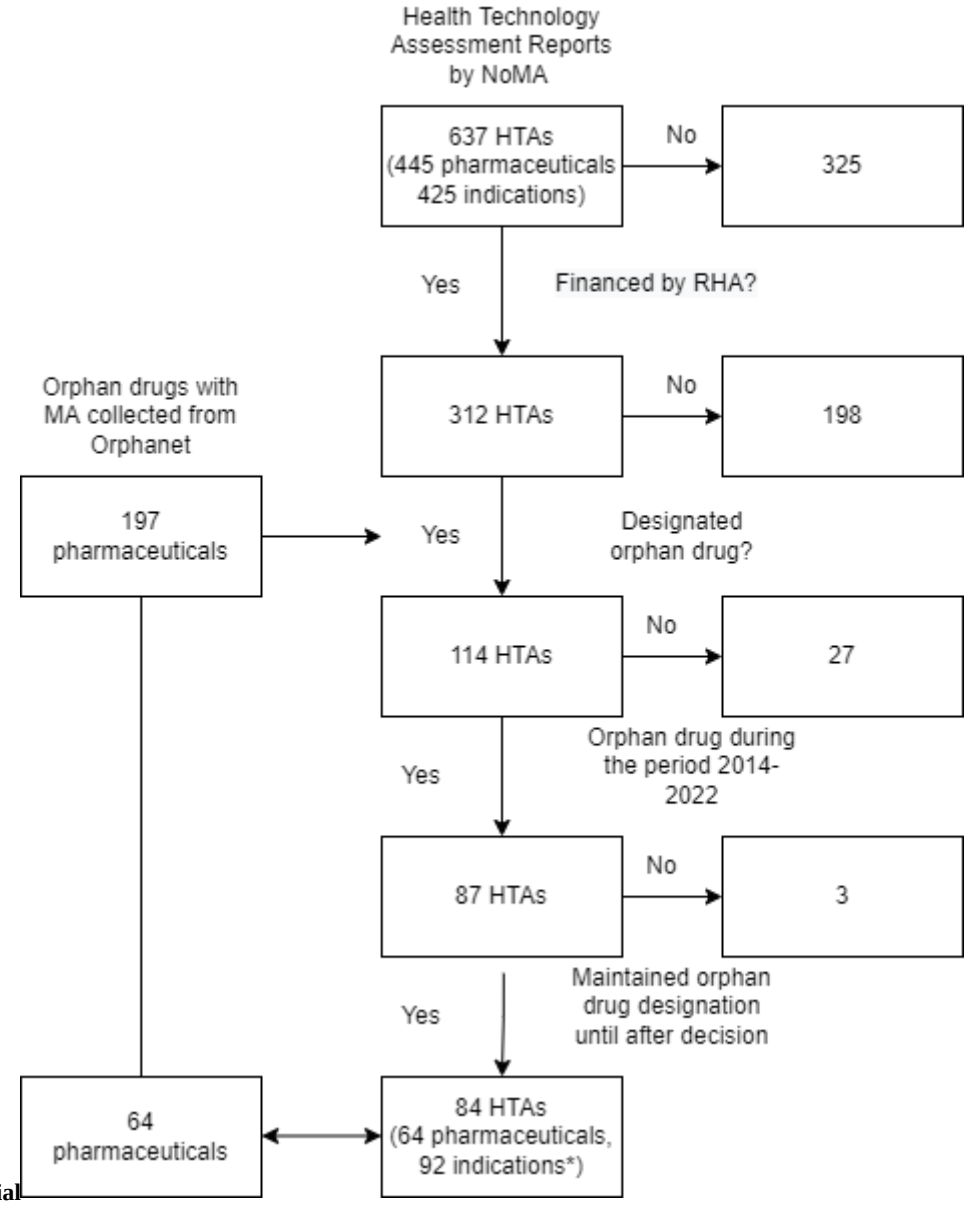


Figure 22 Data material

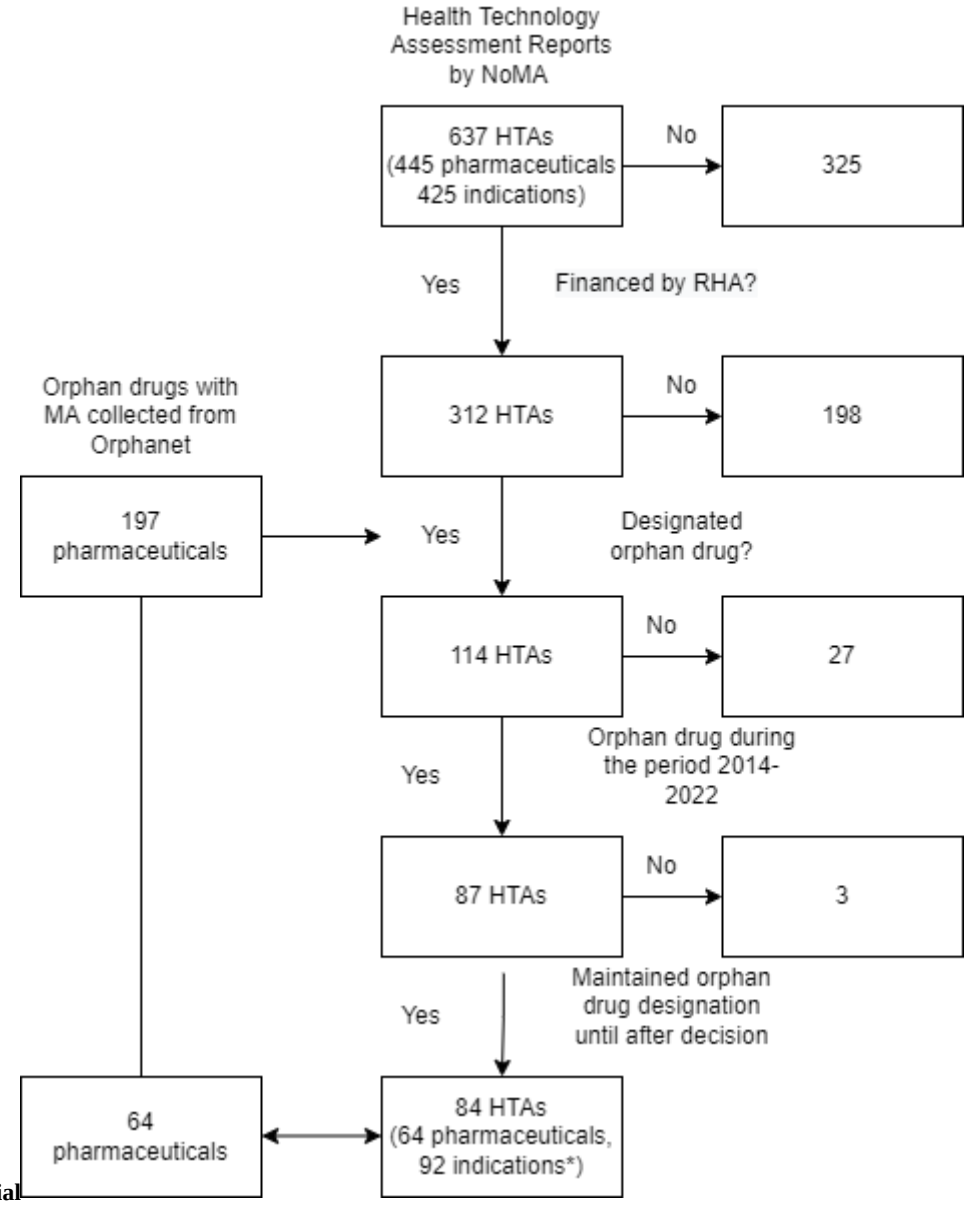
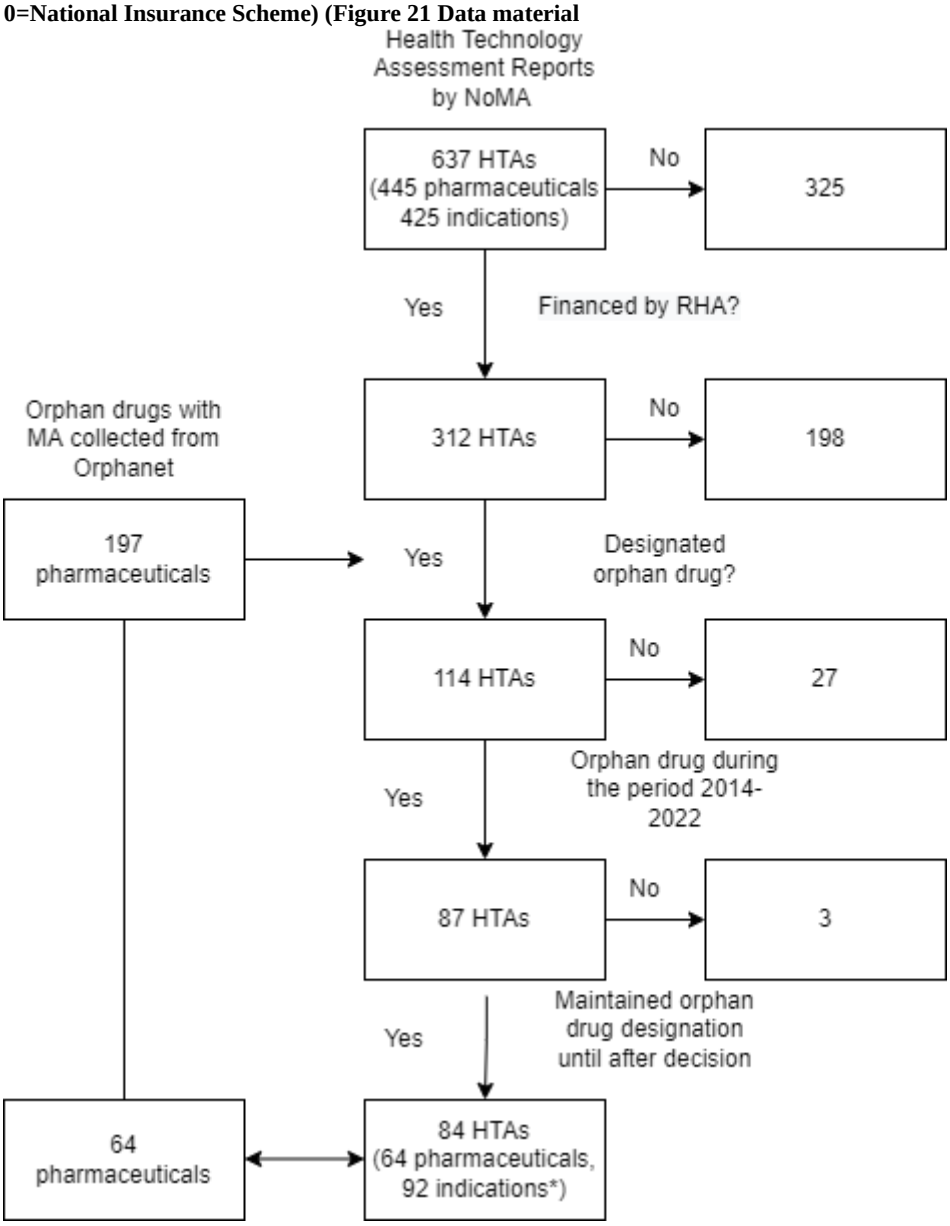


Figure 23 Data material

Figure 24) including those that had their market authorisation and/or orphan drug status withdrawn from a We also collected data on all health technology assessments reports issued by NoMA for medicinal products financed both by Regional Health Authorities and the National Insurance Scheme was collected from the website of NoMA.

First, all assessment reports were coded with respect to financial responsibility (1=Regional Health Authorities, 0=National Insurance Scheme) (Figure 21 Data material



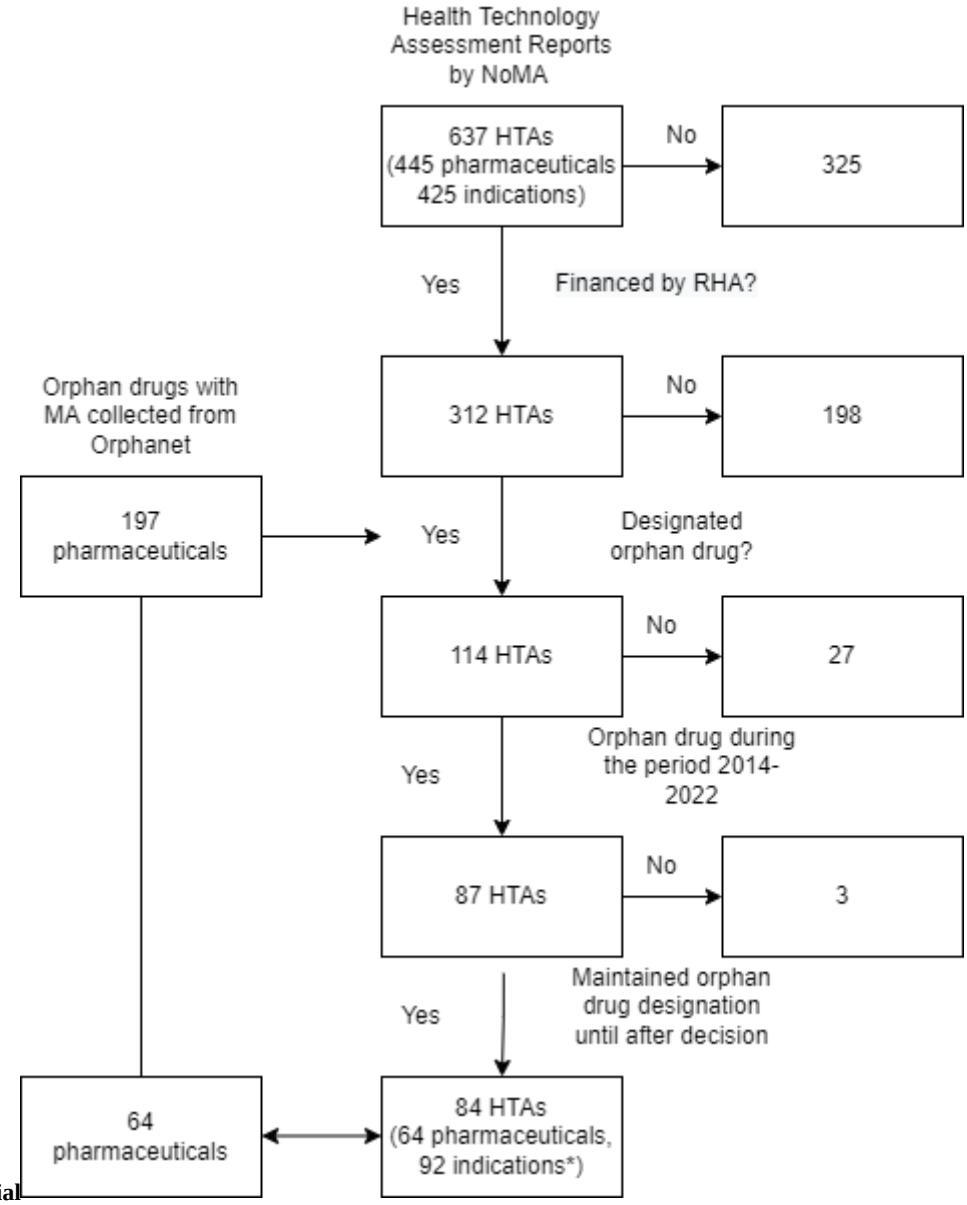


Figure 22 Data material

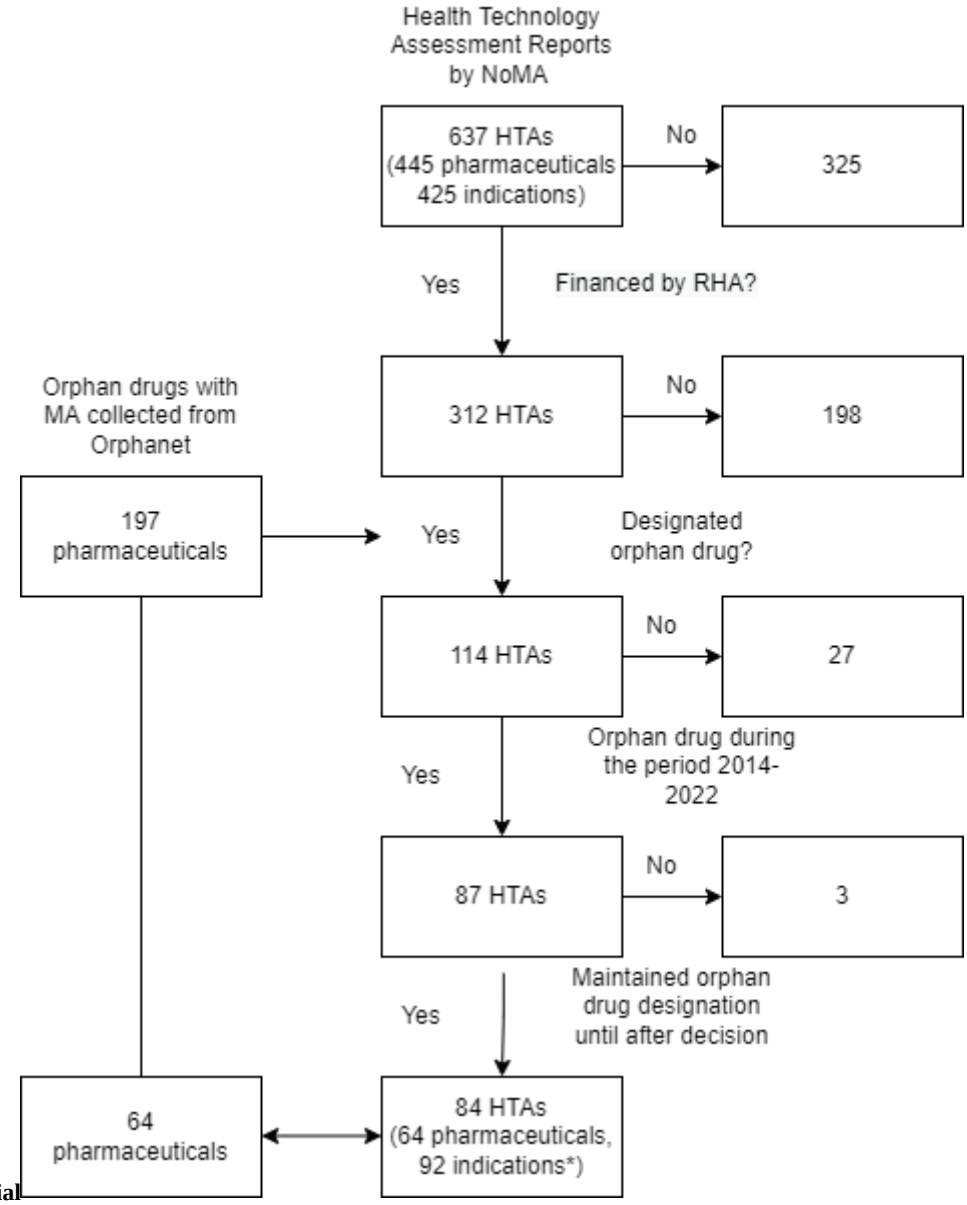


Figure 23 Data material

Figure 24). Assessments were then coded according to if it had an orphan drug designation during the period 2014-2021 (0 = no, 1 = yes). If the medicinal product had its marketing authorisation or orphan drug designation withdrawn, the date of withdrawal was compared to date of decision in Decision Forum. Orphan drugs which had their designation withdrawn before decision was excluded. Cut off points for data collection of HTA reports were set at date

for marketing authorisation date at 30.06.2021. HTAs with pharmaceuticals that were financed

Figure 21 Data material

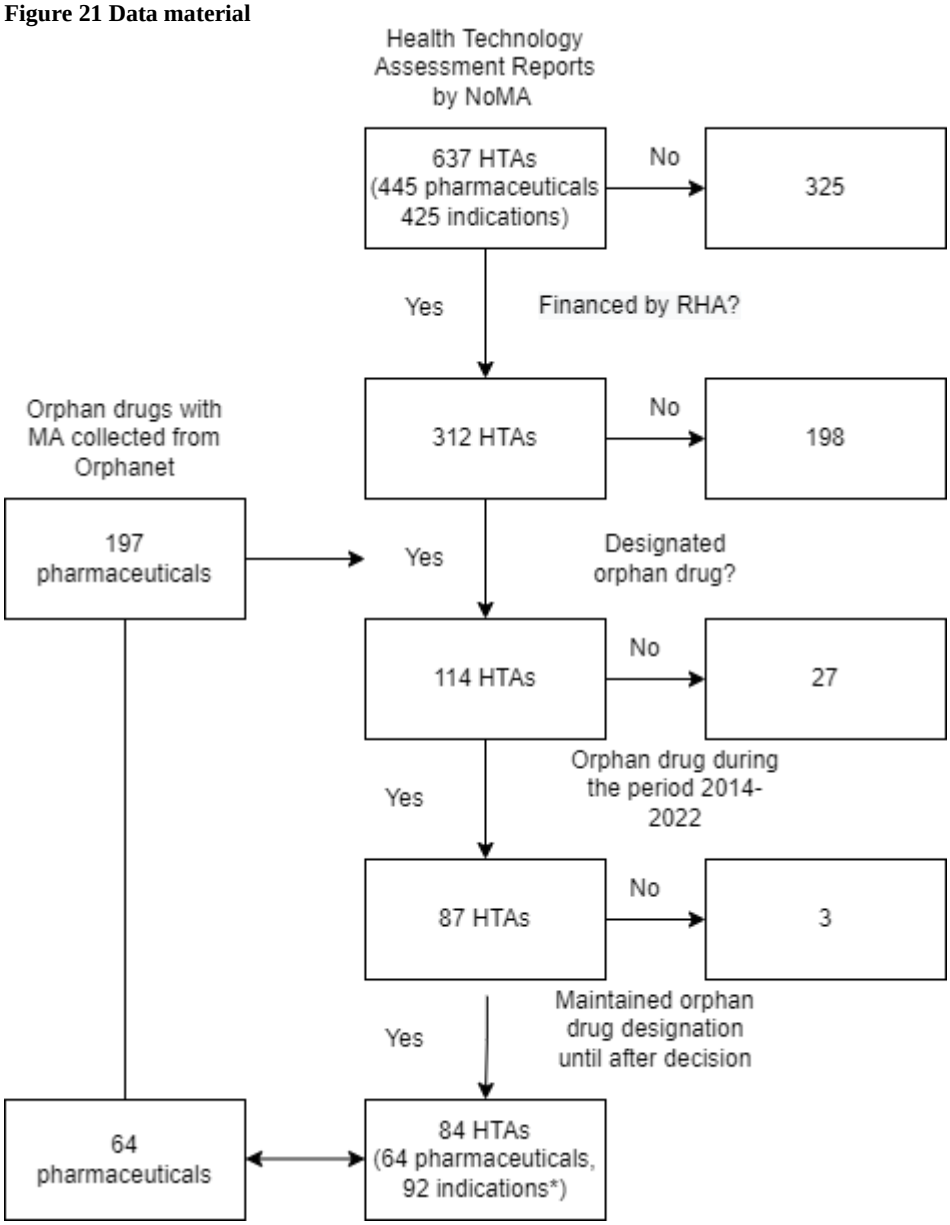
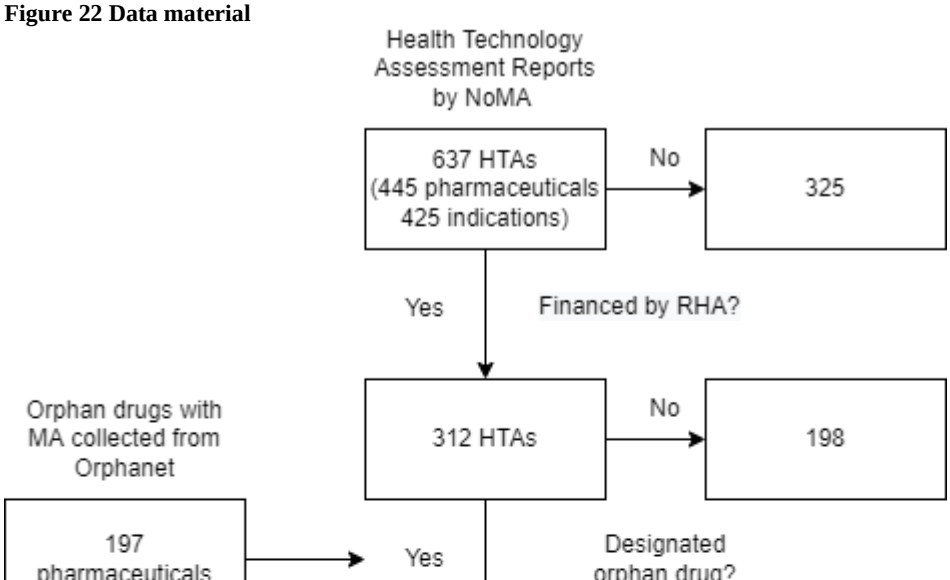


Figure 22 Data material



by the National Insurance Scheme was excluded (n = 325) . Reducing the data material to HTAs financed by Regional Health Authorities (n = 312). By comparing the reduced data material to the list of pharmaceuticals obtained from the report from Orphanet, HTAs with pharmaceuticals that did not have an orphan drug designation was excluded (n = 198). Reducing the data material to 114 HTAs. HTAs with pharmaceuticals that were not designated as an orphan drug in the period 2014-2021 (n= 27) were excluded, leaving 87 HTAs for further screening. The HTAs with pharmaceuticals which had their orphan drug designation withdrawn was investigated with respect to date of withdrawal of designation and decision date by Decision Forum. This led to exclusion of 3 HTAs of which pharmaceuticals had their orphan drug designation withdrawn before the date of decision in Decision Forum. Finally, duplicates of HTAs (i.e. a pharmaceutical had a prior HTA on the same indication which was updated with a new report) were excluded from the dataset (n = 2). Our data material then consisted of 64 unique pharmaceuticals in 82 HTAs, of which 5 HTAs contained either multiple indications or subgroups of rare conditions that were split up, making it a total of 92 indications.

We collected data material from reports performed by NoMA.

Variables

Variables used in data analysis is:

Table 2 Variables used in data analysis

Variable	Variable name	Description
ATC	A: Alimentary tract and metabolism B: Blood and blood forming organs C: Cardiovascular system D: Dermatological G: Genito urinary system and sex hormones H: Systemic hormonal preparations, excluding sex hormones and insulins	ATC is a system for classifying what organ the pharmaceutical is aimed at and the therapeutic effect it has.

Variable	Variable name	Description
	J: Antiinfective for systemic use L: Antineoplastic and immunmodulating agents L01: Treatment of cancer M: Musculo-skeletal system N: Nervous system P: Antiparasitic products, insecticides, and repellents R: Respiratory system S: Sensory organs V: Various	
HTA track	1: Proceed to tendering without estimation of ICER 2: Relative effectiveness and safety 3: Full estimation of ICER 4: Simplified assessment	
Incremental cost	Continuous	Describes the difference in cost between comparator treatment and pharmaceutical under consideration
Cost per patient per year	Continuous	Describes the cost of treating one patient for a year
QALYs gained	Continuous	Describes the expected increase in quality adjusted life years (1 QALY = 1 year of perfect health)

Variable	Variable name	Description
ICER	Continuous	The incremental cost-effectiveness ratio. ICER is the result of dividing incremental cost on QALYs gained.
Population	Continuous	Describes the estimated number of patients intended to treat per year.
Budget impact	Continuous	Describes the incremental budget impact of adopting a new pharmaceutical
Severity of disease	Continuous	Describes the QALYs lost due to the disease or condition
Number of decisions	Discrete	Describes the number of decisions by Decision Forum
Number of negotiations	Discrete	Describes the number of negotiations between the Procurement services for Health Enterprises Ltd and manufacturer
Reimbursement status	Dummy (0=not reimbursed, 1 reimbursed)	Describes the outcome of decision in Decision Forum
Comparator clinical trial	Dummy (0= no comparator, 1= comparator)	Describes if the manufacturer used a comparator in clinical trials. Placebo is coded as using a comparator.
Dates	Marketing Authorisation Horizon Scanning Report submission	Is the date of the events.

Variable	Variable name	Description
	Commissioning Forum	
	Start of HTA report	
	Completion of HTA report	
	Decision Forum	

Descriptive statistics (Table 3) was developed using Excel. Discrimination of drugs intended for treatment of cancer was discriminated using ATC level 1 code "L" and ATC level 2 code "01" which identifies antineoplastic agents used in the treatment of cancer (WHO Collaborating Centre for Drug Statistics Methodology, 2021).

Table 3 Descriptive statistics methods (Newbold, Carlson and Thorne, 2013)

Measure	Equation	Description
Mean	$\bar{x} = \frac{1}{n}\left(\sum_{i=1}^{n} x_i\right) = \frac{x_1 + x_2 + \cdots + x_p}{n}$	Describes the central tendency of the data.
Median	$median\ (x) = \frac{x_{(n+1)}}{2}$	Describes the central tendency of the data.
Unique pharmaceuticals	Counting	By counting. Describes how many unique pharmaceuticals used for x conditions (indications).
Total number of indications	Counting	By counting, describes how many indications that have undergone consideration by New Methods. An indication usually is analogous to conditions or subgroups of a condition.
Total number of HTA reports	Counting	By counting. An HTA report is a document assessing the qualities of a pharmaceutical used to treat x condition(s).

Measure	Equation	Description
Total budget impact	$\sum_{i=1}^{n} x_i$	Describes the total impact on Regional Health Authorities budget.
Total burden of disease	$\sum_{i=1}^{n} (x_i\, y_i)$	Describes the total burden of disease by multiplying absolute shortfall (measure of burden of disease) by the patient population intended to treat.
QALYs gained	$\sum_{i=1}^{n} (x_i\, y_i)$	Describes the gain in quality adjusted life years. For the total population we find the total QALYs gained by multiplying the mean gains in QALY for the individual condition by the patient population intended to treat.
Population intended to treat	$\sum_{i=1}^{n} x_i$	Describes the number of patients intended to treat. We compute the total population intended to treat by summing the total,
Time	$\sum_{i=0,1}^{d} d_0 - d_1$	Describes elapsed time in days for specific events (Marketing Authorisation, decision date etc.). NoMA reports performance time on HTAs, from they start working on it until completion. Other computation of time is done by subtracting the start date from the end date.

Measure	Equation	Description
Quartiles	$Q(x) = q_x(n+1)$	Describes the distribution of the data by quartiles (the 25% value, 50% value etc.).
Differences	$difference = x - y$	Describes the difference between two estimates.

We performed one groupings of decisions, one with respect to the White paper on priority setting with decisions grouped to 2014-2018 and 2019-2021.

Visual inspection of the data revealed non-normal distribution with leftward skewness with no extreme outliers in the dataset. Summary statistics (**Error! Reference source not found.**) r evealed heteroscedasticity in the dataset.

Mann-Whitney U test

The Mann-Whitney U test is a nonparametric test used to determine if the central location of two population distributions are the same (Newbold, Carlson and Thorne, 2013). Data is ranked (x=1,2,…,x) without consideration of which sample they belong. The distribution of the Mann-Whitney statistic, U, approaches normal distribution for large samples (>10), and is compared with the normal distribution. The test statistics is given by

Equation 1 (Newbold, Carlson and Thorne, 2013)

$$\boldsymbol{U = n_1 n_2 + \frac{n_x(n_x+1)}{2} - R_x.}$$

Where n_x=number of observations in the sample and R_x is the lowest rank sum of the two populations. The expected mean is given by

Equation 2 (Newbold, Carlson and Thorne, 2013)

$$E(U) = \mu_U = \frac{n_1 n_2}{2},$$

and the variance

Equation 3 (Newbold, Carlson and Thorne, 2013)

$$Var(U) = \sigma_U^2 = \frac{n_1 n_2 (n_1 + n_2 + 1)}{12}$$

and the Z-statistics

Equation 4 (Newbold, Carlson and Thorne, 2013)

$$Z = \frac{U - \mu_U}{\sigma_U}$$

Two sample test of proportions

We can then use a two-sample test of proportions to test for difference between the populations. The test uses an asymptotically normally distributed test statistics computed as

Equation 5 (Stata, 2022)

$$z = \frac{\widehat{p_1} - \widehat{p_2}}{s_{d0}}$$

where

Equation 6 (Stata, 2022)

$$s_{d0} = \sqrt{\widehat{p_p}\widehat{q_p}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}$$

is the standard error of $\widehat{p_1} - \widehat{p_2}$ under the null hypothesis that $p_1 = p_2$, with

Equation 7 (Stata, 2022)

$$\widehat{p_p} = \frac{x_1 + x_2}{n_1 + n_2}$$

Equation 8 (Stata, 2022)

and $\widehat{q_p} = 1 - \widehat{p_p}$.

The confidence interval is given by

Equation 9 (Stata, 2022)

$$(\widehat{p_1} - \widehat{p_2}) \pm z_{1-a/2}\sqrt{s_1^2 + s_2^2}$$

where $s_1 = \frac{\sqrt{\widehat{p_1}\widehat{q_1}}}{n_1}$ and $s_2 = \frac{\sqrt{\widehat{p_2}\widehat{q_2}}}{n_2}$ are the standard error of the two sample proportions and $z_{1-\alpha/2}$ is the $(1 - \alpha/2)$th quantile of the normal distribution. We will use a standard confidence interval of 95%.

Logistic regression

Keeping in view that the dependent variable is reimbursement, which is a dummy variable (1 if reimbursed, 0 if not reimbursed). Among the alternative dummy or binary choice regression models we can experiment the logistic and the probit regression models. As the data and some of the scatterplots indicate that the relationships between the variables have a pattern of heteroscedasticity, so it will be a fairly good idea to estimate the logistic or the probit model with robust standard errors. As logistic regression is more known, our choice falls on a logistic regression model.

The logit of the multiple logistic regression model is given by (Hosmer, Lemeshow and Sturdivant, 2013)

Equation 10 (Hosmer, Lemeshow and Sturdivant, 2013)

$$g(x) = \ln\left(\frac{\pi(x)}{1-\pi(x)}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p$$

The conditional probability that the outcome is present denoted by $\Pr(Y = 1|x) = \pi(x)$ (Hosmer, Lemeshow and Sturdivant, 2013). And the logistic is given by

Equation 11 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\pi(x) = \frac{e^{g(x)}}{1 + e^{g(x)}}$$

We will fit the model using estimates of the vector $\boldsymbol{\beta}' = (\beta_0, \beta_1, \beta_2 \ldots \beta_p)$ by maximum likelihood (Hosmer, Lemeshow and Sturdivant, 2013). The likelihood function is given by the equations

Equation 12 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\sum_{i=1}^{n} [y_i - \pi(x_i)] = 0$$

and

Equation 13 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\sum_{i=1}^{n} x_{ij}[y_i - \pi(x_i)] = 0$$

$j = 1, 2, 3, \ldots, p$. We will have likelihood equations equal to $p + 1$ by differentiating the log-likelihood function with respect to the $p + 1$ coefficients (Hosmer, Lemeshow and Sturdivant, 2013). Solutions for the equations will be denoted as $\hat{\beta}$ and so the values fitted in the multiple logistic regression model are $\hat{\pi}(x_i)$ and the value of the expression in Equation 11 is computed using $\hat{\beta}$ and x_i.

Confidence intervals for the slope coefficient are calculated by

Equation 14 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\hat{\beta}_1 \pm z_{1-\frac{a}{2}}\widehat{SE}(\hat{\beta}_1)$$

and for the intercept

Equation 15 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\hat{\beta}_0 \pm z_{1-\frac{a}{2}}\widehat{SE}(\hat{\beta}_0).$$

We obtain the variance and covariance of the estimated coefficients from the matrix of the second partial derivative of the log likelihood function (Hosmer, Lemeshow and Sturdivant, 2013). The partial derivatives can in general be written as

Equation 16 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\frac{\partial^2 L(\beta)}{\partial \beta_j^2} = -\sum_{i=1}^{n} x_{ij}^2 \pi_i (1 - \pi_i)$$

Equation 17 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\frac{\partial^2 L(\beta)}{\partial \beta_j \partial \beta_1} = -\sum_{i=1}^{n} x_{ij} x_{ij} \pi_i (1 - \pi_i)$$

for $j, l = 0,1,2 \ldots, p$ where π_i denotes $\pi(x_i)$. Let the $(p + 1) \times (p + 1)$ matrix containing the negative of the terms given in equation 17 and 18 be denoted as $I(\beta)$ (Hosmer, Lemeshow and Sturdivant, 2013). From the inverse of matrix, denoted as $Var(\beta) = I^{-1}(\beta)$, we obtain the

variance and covariance of the estimated coefficients. The notation $Var(\beta_j)$ denotes the *j*th diagonal of the matrix which is the variance of $\widehat{\beta_j}$ and the covariance $Cov(\beta_j, \beta_l)$, because it is impossible to write a general expression of the matrix. By evaluating $Var(\beta)$ at $\hat{\beta}$. $\widehat{Var}(\hat{\beta}_j)$ and $\widehat{Cov}(\hat{\beta}_j, \hat{\beta}_l)$ we obtain the variance and covariance, denoted as $\widehat{Var}(\hat{\beta})$. $j, l = 0,1,2 \dots p$ denotes the value in the matrix (Hosmer, Lemeshow and Sturdivant, 2013). The standard error of the coefficients is denoted as

Equation 18 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\widehat{SE}(\hat{\beta}_j) = \left[\widehat{Var}(\hat{\beta}_j)\right]^{1/2}$$

for $j = 1,2,3, \dots, p$. The univariable Wald test statistics (z) is given by the equation

Equation 19 (Hosmer, Lemeshow and Sturdivant, 2013)

$$W_j = \frac{\widehat{\beta_j}}{\widehat{SE}(\hat{\beta}_j)}$$

which, under the hypothesis that the individual coefficient is zero, will follow a normal distribution.

Model building

We will build model(s) by purposeful selection. We apply the steps of building a model by *purposeful selection* following the approach suggested by Hosmer, Lemeshow and Sturdivant (2013).

First a univariate analysis of each independent variable is performed. We employ a significance level of 0.25 in this step, avoiding leaving out variables that can prove significant in later steps. For dummy and categorical variables, we use contingency table analysis of the outcome (y=0, 1) versus the k levels of the independent variable. We apply a Pearson chi-square test which is asymptomatically equivalent to the likelihood ratio chi-square test and is used to assess the significance of coefficients.

For continuous variables we fit a univariable logistic regression model to obtain estimated coefficients, standard error, likelihood ratio test for the significance of the coefficient and the univariable Wald statistics. As log likelihood is given by Stata, we find the G-test statistics by Equation 20, where the test statistics G is compared with the $k - 1$ degrees of freedom for the Chi-square distribution.

Equation 20 (Hosmer, Lemeshow and Sturdivant, 2013)

$$G = -2(likelihood\ without\ the\ variable - likelihood\ with\ the\ variable$$

As several of the variables are multicollinear, we only include one variable for each category (incremental costs, QALYs gained etc.) (Hosmer, Lemeshow and Sturdivant, 2013). Multivariable models will be built separately for NoMA and manufacturers using their respective estimates of costs and QALYs gained. Other variables will be used in both models. In this step we reduce the level of significance, as the sample is small in nature and data is missing, we consider it to be unfair to employ a significance level of 0.05, and so we employ a slightly higher level of significance at 0.1. Removing variables with the highest p-value except variables that is considered critical, we find the smallest possible model.

Coefficients from the small model is compared with the coefficients from the bigger model to identify coefficients that has changed more than 20% (Hosmer, Lemeshow and Sturdivant, 2013). Coefficients that were removed causing the change in coefficients of >20% is placed back into the model. We consider these coefficients to provide adjustment of the variables in the small model. We continue cycling this step until all variables that are statistically significant and considered important for the model.

Variables excluded in the first step is then added back into the model and evaluated by p-value ≤0.1 (Hosmer, Lemeshow and Sturdivant, 2013). For each continuous variable, we run Lowess smoothing plot (Equation 21) with default bandwith 0.8 and transform the dependent variable to logit to check for linearity. Since the sample is small, we relax the requirement to absolute linearity. Following this we "lock" our model and will not remove any main effects.

Equation 21 (Hosmer, Lemeshow and Sturdivant, 2013)

$$w(x_i, x_j) = \left[1 - \left(\frac{|x_i x_j|^3}{\Delta}\right)^3\right]$$

The model is then fitted with interaction term(s) that seem plausible and of practical importance (Hosmer, Lemeshow and Sturdivant, 2013). Following this we remove interaction terms with the highest p-value one at the time. Note that interaction terms considered as important in explaining reality remains in the model. We are then left with a model with variables that is

statistically significant (0.1) and/or of practical importance. Statistically significance of the model is tested by using a likelihood ratio test as described above.

Goodness of fit

Finally, we assess the goodness of fit for the entire model by employing a classification table. As the classification table has received some critiques (Hosmer, Lemeshow and Sturdivant, 2013) we will evaluate goodness of fit with two additional tests: Hosmer-Lemeshow test and Area Under the Receiver Operating Characteristics (ROC) Curve.

The classification table measures the goodness of fit by "cross-classifying the outcome variable *y* with a dichotomous variable whose values are derived from the estimated logistic probabilities" (Hosmer, Lemeshow and Sturdivant, 2013). It produces four different combinations of predicted and actual values (Table 4).

Table 4 Classification table of actual and predicted outcome.

		Actual	
Predicted		Reimbursed	Not reimbursed
	Reimbursed	True positive	False positive
	Not reimbursed	False negative	True negative

Applying the values from the table, we calculate sensitivity (the models ability to correctly classify positive decisions, "reimbursed"), and specificity (the models ability correctly classify negative decisions, "not reimbursed"). In the table we apply the default cut-off value of 0.5.

Equation 22 (Hosmer, Lemeshow and Sturdivant, 2013)

$$Sensitivity = \frac{TP}{TP + FP}, specificity = \frac{TN}{TN + FN}$$

True rates are calculated using the classification table (Hosmer, Lemeshow and Sturdivant, 2013). *True positive rate* explains if a pharmaceutical is predicted to be reimbursed given that it actually is reimbursed while *true negative rate* explains if a pharmaceutical is predicted to "Not be reimbursed" given that it actually is not reimbursed.

Equation 23 (Hosmer, Lemeshow and Sturdivant, 2013)

$$True\ positive\ rate = \frac{TP}{TP + FN}, True\ negative\ rate = \frac{TN}{TN + FP}$$

Pearson's Chis-Square Statistics is well known as a statistical test to investigate goodness of fit. The fitted values are calculated for each covariate pattern and depend on the estimated probability for covariate pattern (Hosmer, Lemeshow and Sturdivant, 2013). The fitted value for the *j*th covariate pattern is denoted $\hat{y}_j$:

Equation 24 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\hat{y}_j = m_j\hat{\pi}_j = m_j\left\{\frac{e^{\hat{g}(x_j)}}{1+e^{\hat{g}(x_j)}}\right\}$$

Where $\hat{g}(x_j) = \hat{\beta}_0 + \hat{\beta}_1 x_1 + \hat{\beta}_2 x_2 + \cdots + \hat{\beta}_p x_p$. We calculate the particular Pearson residual:

Equation 25 (Hosmer, Lemeshow and Sturdivant, 2013)

$$r(y_j, \hat{\pi_j}) = \frac{y_j - m_j\hat{\pi}_j}{\sqrt{m_j\hat{\pi}_j(1-\hat{\pi}_j)}}$$

And the summary statistic based on this is the Pearson chi-square statistic:

Equation 26 (Hosmer, Lemeshow and Sturdivant, 2013)

$$X^2 = \sum_{j=1}^{J}\left[r(y_j, \hat{\pi}_j)\right]^2$$

X^2 is the likelihood ratio test statistics The distribution of X^2 is chi-square with degrees of freedom equal to $J-(p+1)$ under the assumption that the fitted model is correct in all aspects. As it is probable that J≈n, and Stata does not allow Pearson chi-square to be collapsed, we will use the Hosmer-Lemeshow test which allows us to collapse the values of estimated probabilities. With a sufficient sample size we can collapse the estimated probabilities into 10 groups, as our sample size is quite small we will use a smaller number of groups. Hosmer, Lemeshow and Sturdivant (2013) states that the conservative view on collapsed groups of estimated probabilities should consists of frequencies >5, but Hosmer, Lemeshow and Sturdivant relaxes this assumption. Still, simulations using the Hosmer-Lemeshow test shows that using less than 6 groups usually estimates a good fit regardless of the actual fit of the model. We therefor employ a moderate number of groups of 7. The Hosmer-Lemeshow statistics is obtained by:

Equation 27 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\hat{C} = \sum_{k=1}^{g} \left[\frac{(o_{1k} - \hat{e}_{1k})}{\hat{e}_{1k}} + \frac{(o_{0k} - \hat{e}_{0k})}{\hat{e}_{0k}} \right],$$

Where

Equation 28 (Hosmer, Lemeshow and Sturdivant, 2013)

$$o_{1k} = \sum_{j=1}^{c_k} y_j$$

$$o_{0k} = \sum_{j=1}^{c_k} (m_j - y_j)$$

$$\hat{e}_{1k} = \sum_{j=1}^{c_k} m_j \hat{\pi}_j,$$

$$\hat{e}_{0k} = \sum_{j=1}^{c_k} m_j (1 - \hat{\pi}_j)$$

And c_k is the number of covariate patterns in the group in the *k*th group (Hosmer, Lemeshow and Sturdivant, 2013). In general it can be written as

Equation 29 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\hat{C} = \sum_{j=1}^{g} \frac{\left(O_{1k} - n'_k \bar{\pi}_j\right)^2}{n'_k \bar{\pi}_k (1 - \bar{\pi}_k)}$$

Where $\bar{\pi}_k$ is the average estimated probability in the *k*th group,

Equation 30 (Hosmer, Lemeshow and Sturdivant, 2013)

$$\bar{\pi}_k = \frac{1}{n'_k} \sum_{j=1}^{c_k} m_j \bar{\pi}_j$$

The Hosmer-Lemeshow Chi-square statistics with the corresponding p-value will be used to assess the fit of the model (Hosmer, Lemeshow and Sturdivant, 2013). Chi-square should be as low as possible with a corresponding high p-value to explain goodness of fit.

Area under the Receiver Operating Characteristics Curve (ROC), ranging from 0.5 to 1.0 provides a measure of the models' ability to discriminate between the pharmaceuticals that achieve reimbursement and the ones who does not achieve reimbursement (Table 5). Plotting the probability of getting reimbursed (sensitivity) and not getting reimbursed (specificity) for the entire range of cut-off points. As a rule of thumb, area under the curve (AUC) describes the ability to discriminate:

Table 5 Thresholds values of discrimination in Receiver Operating Characteristics Curve (Hosmer, Lemeshow and Sturdivant, 2013)

AUC	Explanation
=0.5	No discrimination
0.5<ROC<0.7	Poor discrimination
0.7≤ROC<0.8	Acceptable discrimination
0.8≤ROC<0.9	Excellent discrimination
0.9≤ROC	Perfect discrimination

As our data sample is limited, we will accept 0.5<ROC as satisfactory.

Software

All computations on logistic regression, Mann Whitney U-test and Test of sample proportions will be performed using Stata SE 17. Descriptive statistics are developed using Excel.

Results

EMA/European Commission had granted orphan drug designation and marketing authorisation to a total of 210 pharmaceuticals by August 2021. Of the 210 pharmaceuticals, 132 had maintained both marketing authorisation and orphan drug designation[1]. Sixty-five pharmaceuticals held a marketing authorisation but had their orphan drug designation withdrawn, mainly because their 10-year exclusivity period had elapsed. Further 13 medicinal products had their marketing authorisation withdrawn for various reasons, mainly because of low sales volumes in Europe.

[1] 1 drug, Skysona, was excluded from the original list due to its marketing authorisation was withdrawn in November 2021.

We identified 637 health technology assessment reports (HTAs)[2] performed for the Regional Health Authorities and the National Insurance Scheme by NoMA at the time of data extraction (April 10, 2022). Of the 637 HTAs, 312 HTAs on pharmaceuticals were financed by the Regional Health Authorities. 114 of the 312 HTAs had medications that had been granted Orphan Drug Designation by EMA. 30 HTAs of the 114 HTAs was on pharmaceuticals that did not have a valid orphan designation in the period 2014-2021 or lost it prior to decision. 84[3] of the HTAs on 64 pharmaceuticals was included in the dataset which had maintained their orphan drug designation. Decisions had been made on 76 out of the 84 HTAs.

The indication was cancer for 47 HTAs (30 unique pharmaceuticals) of the 84 HTAs, while the remaining 37 (34 unique pharmaceuticals) were related to various other rare diseases. Of the 84 HTAs, 45 HTAs on 35 pharmaceuticals had received a favourable decision in Decision Forum by the end of 2021. 27 (19 unique pharmaceuticals) of the 45 positive decisions were for cancer, and the remaining 18 (15 unique pharmaceuticals) for other conditions.

A total of 67 of the current 132 drugs collected from Orphanet with orphan drug designation and marketing authorisation were reimbursed through National Health Insurance or the Regional Health Authorities. For drugs that had their orphan drug designation withdrawn but retained their marketing authorisation, 46 out of 55 unique drugs were reimbursed.

Burden of disease

The burden of disease ranged from 35,640 QALYs to 52,701 QALYs (Table 6) for 49 rare diseases (Appendix 4). The burden of "orphan" cancer ran from 7308 to 13,880 QALYs, while it was 24239 to 42693 QALYs for non-cancer.

[2] A drug can have several HTAs, an HTA can cover several indications (conditions) or subtypes of a condition.
[3] 5 HTA reports were split in the dataset as they had different data for different conditions or subtypes of the condition making it a total of 92 "indications".

Table 6 Total and per person burden of disease (QALYs lost) for 49 conditions in which orphan drugs were under consideration by New Methods in quality adjusted life years.

	Low estimate of QALYs lost (Mean QALYs lost per person)	High estimate of QALYs lost (Mean QALYs lost per person)
Low population estimate 1. year – all conditions (1721 patients)	**41256 (23.5)**	**50113 (28.5)**
High population estimate 1. year – all conditions (1928 patients)	**43591 (22.2)**	**52701 (26.8)**
Low population estimate 5. year – all conditions (1612 patients)	**35640 (20.8)**	**37882 (22.1)**
High population estimate 5. year – all conditions (1800 patients)	**37705 (19.8)**	**40207 (21.1)**
Low population estimate 1. year – cancer (543 patients)	**7308 (10.1)**	**7420 (10.2)**
High population estimate 1. year – cancer (748 patients)	**9624 (10.3)**	**9989 (10.7)**
Low population estimate 5. year – cancer (839 patients)	**11400 (11.3)**	**11715 (11.6)**
High population estimate 5. year – cancer (1016 patients)	**13311 (11.1)**	**13880 (11.6)**
Low population estimate 1. year - non-cancer (1213 patients)	**33948 (32.9)**	**42693 (41.3)**
High population estimate 1. year - non-cancer (1215 patients)	**33967 (33.1)**	**42712 (41.6)**
Low population estimate 5. year - non-cancer (877 patients)	**24239 (34.4)**	**26166 (37.1)**
High population estimate 5. year - non-cancer (888 patients)	**24394 (34.4)**	**26327 (37.1)**

Processing time

The mean time from marketing authorisation by EMA to decision in Decision Forum was 795 days over the whole period, varying by year (Table 7), with the longest mean time from MA to decision in 2015 and, by necessity, the shortest in 2021. The shortest mean self-reported processing time for HTA reports was in 2020, with 183.6 days and an overall mean of 226 days. The mean time from marketing authorisation to the decision was 835 days for drugs intended for cancer patients and 733 days for non-cancer patients. (Times for all HTAs are in Appendix 2 – Table describing processing time by indication)

Table 7 Number of indications, the average time from MA to decision and performance time on HTA reports by year of MA.

Year	Number of indications with OD designation authorised by EMA	Mean time from market authorisation to decision	Mean HTA report processing time by HTA year
2014	9	777	258
2015	7	944	191
2016	8	584	205
2017	11	931	375
2018	17	585	209
2019	7	601	209
2020|	10	429	184
2021	4	256	201

Quality adjusted life years gained

The total QALY benefit of the 41/42 orphan indications (missing data) ranged from 3302 to 5417 (Table 8). For cancer, the QALY benefits were 353-649 according to NoMA and 640-1041 according to the manufacturers. The mean QALY gain per patient was estimated at 2.22 by NoMA and 3.30 by the manufacturer (difference 1.07) with medians of 1.07 and 1.94, respectively (difference 0.8) (Table 9 Table 10) (all estimates in **Appendix 3**).

Table 8 Estimated QALY gained by extreme value estimates of population and effect (QALY) by first and fifth year for total population, cancer and non-cancer[4]

Population estimates by year (all estimates by NoMA)	Low QALY estimates NoMA (Mean per person)	Low QALY estimates manufacturer (Mean per person)	Difference (NoMA-manufacturer) (Difference in mean per person)	High QALY estimates NoMA (Mean per person)	High QALY estimates manufacturer (Mean per person)	Difference (NoMA-manufacturer) (Difference in mean per person)
Low population 1. year – total population (1757) patients)	3302 (1.9)	5064 (2.9)	-1762 (-1.0)	3367 (1.9)	5257 (3.0)	-1890 (-1.1)
High population 1. year – total population (1964 patients)	3422 (1.7)	5224 (2.7)	-1802 (-0.9)	3487 (1.8)	5417 (2.8)	-1930 (-1.0)
Low population 5. year – total population (1717 patients)	3332 (1.9)	4648 (2.7)	-1316 (-0.8)	3427 (2.0)	4797 (2.8)	-1370 (-0.8)
High population 5. year – total population (1905 patients)	3461 (1.8)	4828 (2.5)	-1366 (-0.7)	3556 (1.9)	4977 (2.6)	-1421 (-0.7)
Low population 1. year – cancer (543 patients)	353 (0.6)	640 (1.2)	-287 (-0.5)	390 (0.7)	658 (1.2)	-267 (-0.5)
High population 1. year – cancer (748 patients)	460 (0.6)	786 (1.1)	-326 (-0.4)	498 (0.7)	804 (1.1)	-306 (-0.4)
Low population 5. year – cancer (839 patients)	479 (0.6)	902 (1.1)	-423 (-0.5)	564 (0.7)	920 (1.1)	-356 (-0.4)
High population 5. year – cancer (1016 patients)	564 (0.6)	1023 (1.0)	-459 (-0.5)	649 (0.6)	1041 (1.0)	-392 (-0.4)
Low population 1. year - non-cancer (1214 patients)	2950 (2.4)	4424 (3.6)	-1475 (-1.2)	2977 (2.5)	4599 (3.8)	-1623 (-1.3)
High population 1. year - non-cancer (1215 patients)	2962 (2.4)	4438 (3.7)	-1476 (-1.2)	2989 (2.5)	4613 (3.8)	-1624 (-1.3)

[4] There are 41 observations in all NoMA estimates, and 42 observations in manufacturer estimates.

Population estimates by year (all estimates by NoMA)	Low QALY estimates NoMA (Mean per person)	Low QALY estimates manufacturer (Mean per person)	Difference (NoMA-manufacturer) (Difference in mean per person)	High QALY estimates NoMA (Mean per person)	High QALY estimates manufacturer (Mean per person)	Difference (NoMA-manufacturer) (Difference in mean per person)
Low population 5. year - non-cancer (878 patients)	2853 (3.3)	3745 (4.3)	-892 (-1.0)	2863 (3.3)	3877 (4.4)	-1014 (-1.2)
High population 5. year - non-cancer (889 patients)	2898 (3.3)	3805 (4.3)	-907 (-1.0)	2907 (3.3)	3936 (4.4)	-1029 (-1.2)

Table 9 Means and medians, and difference of estimated QALY gains by NoMA and manufacturer.

	Mean of QALY gain (NoMA)	Mean of QALY gain (manufacturers)	Difference (NoMA-man)	Median QALY gain by NoMA	Median of QALY gain by manufacturers	Difference (NoMA-man)2
Low estimates of QALYs	2.21	3.25	-1.05	1.07	1.89	-0.82
High estimates of QALYs	2.26	3.34	-1.08	1.11	1.94	-0.83
Mean estimates of QALYs	2.22	3.30	-1.07	1.07	1.94	-0.87

Table 10 Quartiles for the mean estimated effect of treatment measured in QALYs and difference

Quartiles of estimated QALY gain	Mean **estimates of QALY gain by NoMA**	Mean **estimates of QALY (manufacturer)**	**Diff (NoMA-man)**
0	0.037	0.045	-0.008
0.25	0.536	0.9	-0.364
0.5	1.065	1.935	-0.87
0.75	2.73125	4.0975	-1.36625
1	12.6	18.8	-6.2

Budget impact

The total budget impact in the fifth year following adoption for 58 HTAs was NOK 3.24 billion based on current prices (Table 11), with a mean of NOK 49.1 million and a median of NOK 19.3 million (Table 12). The total budget impact across 28/31 HTAs was highest for non-cancer, adding up to NOK 2.2 billion; for cancer, the budget highest total budget impact was 1.04 billion. Sixty of the indications had a budget impact of less than NOK 100 million; of these, only 30 were reimbursed.

Table 11 Total budget impact for all treatments, cancer and non-cancer estimated for low and high estimates in the first- and fifth year.

	All HTAs (n HTAs/patients)	Reimbursed HTAs (n HTAs/ patients)	Not reimbursed HTAs (n HTAs/patients)
Low total budget impact 1. Year – all conditions	2,504,929,245 (53/1856)	1,047,236,175 (29/1092)	1,457,693,071 (24/601)
High total budget impact 1. year – all conditions	2,832,341,975 (53/1856)	1,233,033,269 (29/1092)	1,599,308,706 (24/601)
Low total budget impact 5. year – all conditions	2,973,729,721 (58/1910)	935,663,260.5 (32/1126)	2,038,066,460 (26/621)
High total budget impact 5. year – all conditions	3,244,173,678 (58/1910)	1,012,247,692 (32/1126)	2,231,925,986 (26/621)
Low total budget impact 1. year – cancer	394,534,075 (31/631)	340,142,760 (17/345)	54,391,315 (14/198)
High total budget impact 1. year – cancer	498,437,753 (31/631)	358,930,543 (17/345)	139,507,210 (14/198)
Low total budget impact 5. year – cancer	639,709,420 (33/663)	401,229,965 (19/377)	238,479,455 (14/198)
High total budget impact 5. year – cancer	544,194,027 (33/663)	382,336,331 (19/377)	161,857,696 (14/198)
Low total budget impact 1. year – non-cancer	2,110,395,170 (22/1225)	707,093,414 (12/747)	1,403,301,756 (10/403)
High total budget impact 1. year – non-cancer	2,333,904,222 (22/1225)	874,102,725 (12/747)	1,459,801,496 (10/403)
Low total budget impact 5. year – non-cancer	2,334,020,301 (25/1247)	534,433,295 (13/749)	1,799,587,005 (12/423)
High total budget impact 5. year – non-cancer	2,699,979,651 (25/1247)	629,911,360 (13/749)	2,070,068,290 (12/423)

Table 12 Mean and median budget impact for the total population in the first- and fifth-year following decision for high and low estimates. Means for cancer and non-cancer indications.

Mean and median budget impact	Mean - low estimates	Mean - high estimates	Median - low estimates	Median - high estimates
1. year following decision - total population	40,348,916	45,682,935	13,133,596	13,133,596
5. year following decision - total population	44,881,699	49,154,147	19,266,705	19,266,705
1. year following decision - cancer	21,608,142	25,216,715		
5. year following decision - cancer	26,472,296	29,741,125		

1. year following decsion - non-cancer	66,582,028	74,460,229
5. year following decsion - non-cancer	66,994,321	72,254,906

Patients intended to treat

The maximum number of patients (patient population) treated in the fifth year of adoption was estimated at 2294 (Table 13). The mean population size across 64 indications was 35 (median 25), with the smallest population being one and the largest 235.

Table 13 Number of patients intended to be treated in the first- and the fifth year following a decision by high and low estimates for total population, cancer and non-cancer.

Patients intended to be treated	Low estimates	High estimates
1. year following decision – all indications	2031.5	2313.5
5. year following decision – all indications	2021.5	2293.5
1. year following decision - cancer	724	929
5. year following decision - cancer	1008	1195
1. year following decision - non-cancer	1307.5	1384.5
5. year following decision - non-cancer	1013,5	1098.5

The effect of absolute shortfall (burden of illness) on the decision to reimburse orphan drugs

We developed two logistic regression models, one using data from the manufacturers data (model 1) and another using NoMAs data (model 2) to explore determinants of reimbursement decisions (0=not reimbursed, 1=reimbursed). The independent variables of the regression analysis were incremental lifetime treatment costs in thousand Norwegian Kroner (NOK), QALYs gained, the burden of disease, single and multiple arms in clinical trials, and the interaction term between multiple arms in clinical trials and QALYs gained. Incremental cost had a marginal negative effect on the odds of reimbursement (Table 14). The variables "QALYs

gained" and "1< study arms in clinical trial" have opposite effects in the two models. In model 1, the variables previously mentioned are negative because of the interaction term. The interaction term explains a different effect for QALYs gained on the odds of reimbursement when the clinical trial has 1 study arm compared to when it has two or more arms. The burden of disease had a positive effect on the odds of reimbursement in both models. In model 2, QALYs gained and two or more arms in clinical trials had a positive effect on the odds of favourable reimbursement decision.

Table 14 Logistic regression analysis of predictors of reimbursement decisions (0=negative, 1=positive) using data from the manufacturer and NoMA [5]

Regressors	Manufacturer n=38. Odds ratio (p-value)	NoMA n=36. Odds ratio (p-value)
Incremental cost (in thousand NOK)	.9996 (0.008)	.9996 (0.008)
QALYs gained	.506 (0.119)	1.7990 (0.048)
The burden of disease, the high estimate	1.153 (0.006)	1.1574 (0.006)
1< study arms in clinical trial[6]	.1273 (0.343)	5.5326 (0.127)
Interaction between study arms and QALYs gained	3.4792 (0.055)	-

[5]

Goodness of fit and model consolidation estimates		
LR Chi^2	12.09 (df:5)	10.41 (df:5)
p>Chi^2	0.1318	0.0643
Pseudo R^2	0.2373	0.2931
Correctly classified	81.6%	83.33%
Hosmer-Lemeshow chi^2(5)	4.32	7.79
p>chi^2	0.5041	0.1680
Area under the ROC curve	0.7532	0.8125

[6] Dummy variable (0= single arm clinical trial, 1 = two or more arms in clinical trial

Effect on reimbursement decisions of the White paper on prioritisation

The White paper on priority setting in healthcare had a negative effect on reimbursement decisions on orphan drugs at a 10% significance level (p-value: 0.0758) (Appendix table 13).

The number of positive decisions by the Decision Forum increased over time (Table 15), but in relative terms number of positive decisions is considered decreasing.

Table 15 Number of decisions made by the Decision Forum according to outcome (positive or negative decision) and calendar year

Year	Number of positive decisions	Number of negative decisions	Relative number of positive decisions
2014	0	1	0 %
2015	4	0	100 %
2016	3	2	60 %
2017	7	1	88 %
2018	6	4	60 %
Sum 2017-2018	20	8	**71.43 %**
2019	9	2	82 %
2020	2	7	22 %
2021	13	11	54 %
Sum 2019-2021	24	20	**54.55 %**

Incremental costs and QALYs estimates

The estimates of incremental costs contained 84 observations, with 42 observations in each sample. The was no significant difference between NoMA and manufacturers (Mann-Whitney U-test: p=0.6873).

The estimates of QALYs gained contained 102 observations, with 50 estimates by NoMA and 52 estimates by manufacturers. The estimated QALY gain was significantly different for NoMA and manufacturers (Mann-Whitney U-test: z=2.182, p=0.0288).

(All results are available in Appendix 4).

Transfer of financing from NIS to RHA

Following the transfer of 63[7] ATC codes for treating rare diseases (not all pharmaceuticals were transferred) from the National Insurance Scheme to Regional Health Authorities, 60 of 63 ATC codes had pharmaceuticals reimbursed[8].

Number of negotiations

Of the 45 HTAs with a positive reimbursement decision (Table 16), we found that 41 had undergone at least one negotiation[9] process prior to decision while 4 did not undergo price negotiation prior to a positive decision of reimbursement.

Table 16 Number of negotiations per HTA

Number of negotiations	Number of HTAs undergone negotiations by number of negotiations	Number of HTAs with a positive reimbursement decisions
0	6	4
1	58	34
2	11	7
3	5	0
4	1	0

Number of cancer indications

There has been no increase in cancer indications by date of Market Authorisation or by date of decision (Table 17).

Table 17 cancer indications by year of market authorisation and decision in Decision Forum.

Cancer indication per year	By date of Market authorisation	By date of Decision Forum
2014	7	1
2015	8	3
2016	6	4
2017	8	7
2018	6	7
2019	2	6

[7] 64 ATC codes were transferred, but only 63 had pharmaceuticals with MA.
[8] Reimbursement was indicated either by a positive decision in Decision Forum or marked with "H-resept" under reimbursement status in "Felleskatalogen" (April 20. 2022).
[9] Negotiation of price was decided by checking their processing website at nyemetoder.no for price notes and the HTA report for price notes and censored prices/ICERs

2020	3	4
2021	2	11
Total	42	43

Summary of results

As of September 2021, a total of 67 of 132 orphan drugs with market authorisation and listed by Orphanet (a European orphan disease network) with orphan drug designation were accessible through public reimbursement in Norway (Results). Of drugs previously, but not any longer, designated as orphan drugs, 46 out of 55 were reimbursed.

The number of patients intended to be treated was between 2022 and 2314 patients, distributed evenly between cancer- and non-cancer conditions. The total burden of disease was between 35640 and 52701 QALYs (Table 6). The burden of disease was significantly higher for non-cancer condition (mean 10.1-11.6 QALYs) than cancer conditions (mean 32.9-41.6).

On average, it takes more than two years to a decision on reimbursement is made in Norway from the time of marketing authorisation is granted by EMA for orphan drugs (Processing time). The Norwegian Medicines Agency (NoMA) uses, on average, 226 days to finalise a Health Technology Assessment (HTA) for orphan drugs compared to the stated goal of finalising all HTAs within 180 days.

Treatment with orphan drugs for 49 rare diseases and conditions yielded between 3302 (NoMA lowest) and 5417 (manufacturers highest) QALYs total (Table 8). The estimates of QALYs were statistically significantly different (Whitney Mann U-test, p=0.0288), while the difference in treatment cost was not. The total budget impact for 66 indications was NOK 3.24 billion, with a mean of NOK 49.1 million.

The logistic regression analysis on predictors of reimbursement showed a positive effect of burden of disease on the odds (OR: 1.15, p:0.006) (Table 14). Incremental costs (in thousands) had a marginal negative effect (OR: .9996, p:0.008) which we consider reasonable. There was a decrease of positive reimbursement decisions following the White paper on prioritisation. The number of pharmaceuticals accessible after the transfer of financial responsibility from the National Insurance Scheme to the Regional Health Authorities has declined.

Four of 44 orphan indications were approved for reimbursement without prior price negotiations between the manufacturer and health authorities. The number of “orphan” cancer indications did not increase during 2014-2021 (Table 16).

Discussion

This study's results indicate a significant disease burden for patients with rare diseases and conditions in Norway. The mean lifetime lost in QALYs for this patient group is 19.8-28.5 per patient (Table 6). Also, the potential benefit from new orphan treatments is considerable, with a mean gain of 2 QALYs per patient (Table 8). The burden of disease and benefit of orphan drugs is especially the case for non-cancer diseases, with a mean burden of illness of >30 QALYs lost and a mean gain of >2 QALYs. NoMAs' note on small patient populations implies that several pharmaceuticals meet at least one of the priority criteria for increased WTP for QALYs. However, most fail to meet the criterion concerning the total national number of patients, which should be below 50.

The statistical difference between NoMA and manufacturers concerning estimated QALY gained with orphan drugs can lead to distrust between the actors. The difference can be due to the devaluation of the evidence by NoMA or “cherry-picking” by manufacturers. Measures are needed to address uncertainty by evaluating evidence more thoroughly and making arrangements for better risk-sharing. We find support for our results from Moss (2021), who concludes in line with our results when investigating QALY estimates on all pharmaceuticals that underwent HTA in 2014-2020.

It is noteworthy that the reimbursement process in Norway counteracts regulatory processes in EMA and FDA designed to promote rapid access for patients with rare diseases. It is counteracted by delayed submission of documentation by manufacturers and long performance time on HTAs by NoMA, resulting in a mean time from MA to decision of >2 years. We can infer that patients with rare diseases suffer from this delay. Csanádi *et al.* (2018) and Proba samfunnsanalyse (2021) suggest that manufacturers may delay launches in countries with a low WTP. Proba further implies that strict and idiosyncratic requirements regarding documentation by NoMA and New Methods are another factor in the delayed submission of documentation.

NoMA performed most of HTAs on cancer indications, but we did not observe any increase in cancer indications among orphan drugs in the period. The European Union states in the

evaluation of orphan drug Regulation that one-third of all orphan drugs are for cancer treatment (European Commission, 2020). Côté and Keating (2012) argue that this is a lucrative commercial clustering, with cancer drugs among the most profitable. As oncology is considered a branch of its own within medicine, it should be considered beneficial to design a regulatory and reimbursement framework for rare cancers.

The European Union is currently evaluating some of the issues of the current regulatory framework, aiming to reshape the regulatory framework (European Commission, 2020). The European Union aims for a better fit to ensure that the regulatory framework supports the development of pharmaceuticals for genetic disorders where there is no available treatment and high unmet need. For example, it could redefine the criteria for orphan drug designation, such as the prevalence criteria.

New Methods are, according to the data available, applying the priority criteria set in the White paper on prioritisation (Table 14 Incremental costs and burden of disease were statistically significant at the 5% level. The regression coefficient for incremental costs implies an odds ratio close to 1, which we consider reasonable as an increase of NOK 1,000 would not significantly impact the outcome. In model 2 (NoMAs data), QALYs gained increased the odds of reimbursement and are significant at the 5% level, which is in line with the priority criteria. While in model 1 (manufacturers data), QALYs gained had different odds depending on if it was a single-arm clinical trial and two or more arms. As QALYs are on a smaller scale than incremental cost, it is reasonable that an increase in 1 QALY has a more significant impact than a price increase. Nilsen (2021) supports that New Methods efficiently operationalise the priority criteria. While New Methods are applying the priority criteria, there is reason to question if the criteria are applied strictly. The Norheim Commission argues that other factors that can be challenging to quantify, such as life quality of next-of-kin, future productivity and dignity, ought to be considered by decision-makers in line with ICER (NOU 2014:12, 2014).

The results indicate that following the White Paper on prioritisation, there was a decline in positive decisions on reimbursement for orphan drugs. However, transferring financial responsibility from the National Insurance Scheme to Regional Health Authorities in 2019 reduced the number of pharmaceuticals available for patients with rare diseases.

Strengths of this study

Norway has a public system for evaluating and deciding on reimbursement of new technologies, which contributes to transparency as HTA reports and decisions are made

publicly available. Priority criteria are set by the parliament, providing legitimacy to the process.

To our knowledge, this thesis is the first academic paper in Norway addressing market access to orphan drugs. Pharmaceutical associations have done several surveys that are primarily descriptive and general, and they lack a suitable methodology. We examined all orphan drugs considered for reimbursement in Norway by RHAs and conducted statistical tests on the effect of policy changes. The aggregated data on variables used by NoMA in HTAs and Decision Forum to inform decisions are ground-breaking in an academic context. The data generated can inform policymakers of the significant burdens of orphan diseases and the benefits of orphan drugs. Although we did not include non-orphan pharmaceuticals, this thesis can provide insight into the market access landscape for pharmaceuticals in general.

Limitations of this study

A significant limitation is the limited number of HTAs reducing the power of statistical tests. A large amount of missing data also contributes to the lack of statistical power. We investigated only pharmaceuticals that received marketing authorisation as orphan drugs; however, other non-orphan medicines and treatments may be available for patients with rare conditions. Neither did we investigate the accessibility and utilisation of orphan drugs, which is a perspective important for patients with rare diseases.

Some orphan drugs have similar indications, so the aggregated burden of disease, QALYs gained, and other variables may be overfitting our results. We considered it not to be within our expertise to discriminate between similar conditions.

Further research

While this paper investigates access to orphan drugs, we suggest more research on access to treatments for people with rare diseases in Norway and its accessibility. We also recommend research on the prices of pharmaceuticals with discounts from manufacturers.

Policy implications

We recommend that stakeholders go into dialogue to find solutions to reduce the time from Market Authorisation to decision on reimbursement in Norway. Reducing the time from MA to reimbursement is in line with current obligations and commitments at the EU level to ensure the development and accessibility of innovative treatments for patient groups with high unmet needs.

Policymakers at EU level should consider developing special regulatory framework for rare cancer drugs to promote speedy authorisation and appropriate burden of evidence. A unique authorisation track for rare cancer would allow policymakers to provide both orphan drugs and rare cancer drugs with appropriate incentives.

Policymakers should consider looking towards other countries such as England and NHS/NICE and the measures taken there. Uncertainty of the evidence can be addressed by establishing review groups where different experts thoroughly assess the evidence submitted. A key could be establishing an "innovative medicines fund" based on the National Health Service's model. Such a fund can provide rapid access to lifesaving, promote innovative patient treatment, allow for performance-based payment solutions based on Real-World Data, and better risk-sharing. Performance-based payment schemes require that health data (Real World Data) is available for payers and manufacturers, and we consider it urgent to facilitate the use of Real-World Data.

Further, policymakers should consider a broader perspective of costs and effects when assessing orphan drugs as rare diseases often are congenital with onset in early life. Although economists recommend discounting future costs and income in economics, Norway should reconsider the approach to assessing the QALY gain of orphan drugs.

Concluding remarks

Through this thesis, we have explored Norway's market access landscape for orphan drugs. We uncovered a significant disease burden for the rare conditions in which orphan drugs were under consideration and the potential benefit if the drugs were to be adopted. The slow uptake rate of orphan drugs is causing Norway to fall behind in adopting new medical technology; if not corrected, Norway might end up worst in class in healthcare. To address this, Norway should look to the process in other countries, which can increase legitimacy of the process and speed up the adoption of medical technology.

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Appendix 1

System for managed introduction of New Methods in specialized health care in Norway

Decision on reimbursement of new pharmaceuticals in hospitals was decided by the local Health Authorities until 2013 (St. meld 34 (2015-2016), 2016). The mandate of decision was transferred to a national body named "The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway" in 2013 (Nye Metoder, 2022), hereafter referred to as "New Methods". The system was introduced in order to make decision of reimbursement of new methods (pharmaceutical, medical technology, procedures etc.) uniform for all Regional Health Authorities, and provide equal and rapid access for patients (St. Meld 16 (2010-2011), 2010; St. meld. 10 (2012-2013), 2012).

The process in New Methods starts with horizon scanning reports for new health technology and extensions of indication on already reimbursed pharmaceuticals if considered appropriate for HTA (Norwegian Medicines Agency, 2016). The Institute for Public Health are responsible for horizon scanning and issuing reports. The Institute for Public Health cooperates with the Norwegian Medicinal Agency (NoMA) regarding pharmaceuticals (Proba samfunnsanalyse, 2021; Norwegian Medicines Agency, 2016; Lauvrak, 2017). The Norwegian Radiation and Nuclear Safety Authority assists with horizon scanning reports and HTAs when their competence is necessary. Proposals are open for submissions for the public, health care professionals, other bodies, and organisations. Horizon Scanning Reports are not produced for pharmaceuticals that is; considered not to receive public reimbursement; generics for pharmaceuticals that have already been assessed and reimbursed; extension of indication to apply for children when a HTA previously have been produced for adults; other extensions of indication; new amounts of active substances; and new composition that is expected to have minor impact on the patient population intended to treat.

The National Procurement services for Health Enterprises Ltd (Sykehusinnkjøp) holds "pipeline meetings" with the pharmaceutical industry in cooperation with NoMA 24-36 months prior to the expected date of attaining Marketing Authorisation (MA) in Norway (Norwegian Medicines Agency, 2019). Horizon scanning reports are produced six to 12 months before expected MA in Norway (Norwegian Medicines Agency, 2016). Proposals are subject to probing by the actors in cooperation with the Directorate of Health before submission to Commissioning Forum together with consideration of suitability and eventual input for further decision (Proba samfunnsanalyse, 2021). The Norwegian Directorate of

Health decides which of the two actors, Regional Health Authorities or the National Insurance Scheme, should carry the responsibility of financing (Norwegian Medicines Agency, 2016; St. Meld 28 (2014-2015), 2015). Only pharmaceuticals financed by the Regional Health Authorities proceeds to case processing in New Methods while pharmaceuticals financed by the National Health Insurance Scheme undergoes another process. The Norwegian Directorate of Health proposes the assessment track the method should undergo in collaboration with the National Procurement services for Health Enterprises Ltd also (Norwegian Medicines Agency, 2016). Following completion of horizon scanning reports a five week input and preparation phase takes place before case processing in Commissioning Forum commences (Norwegian Medicines Agency, 2016).

Commissioning Forum meets once a month to consider if horizon scanning reports and proposals should proceed to Health Technology Assessment. If a HTA report is commissioned, the Forum decides if the HTA is performed by the Norwegian Institute of Public Health or NoMA. The HTA report can be either a Single Technology Assessment or a Full Health Technology Assessment (St. Meld 28 (2014-2015), 2015). The Commissioning Forum may also decide to request utter information, commission a price note from the National Procurement services for Health Enterprises Ltd or in a few cases propose a mini HTA to be performed by the local Health Authority (Proba samfunnsanalyse, 2021). Assessments on pharmaceuticals (Single Technology Assessments) are delegated to NoMA while HTAs of medical equipment and full HTAs are delegated to the Institute for Public Health (Prop. 55 L, 2019). Commissioning Forum can commission four reports within Single Technology Assessments (Nye Metoder, 2021b). The first option is “competition” which sums up efficacy, safety, patient population intended to treat, placing in chain of treatment and previous shortfall calculations. Second option is “Consideration of relative efficacy” which compares efficacy between a new and old pharmaceutical. Third option is “cost-utility assessment” which estimates severity, utility and resources displaced expressed as an “incremental cost-efficiency ratio” and budget impact. The last option is “other simplification” when the three previous tracks are not suitable or does not add any value, a descriptive summary can be made. Single Technology Assessments and Health Technology assessments, hereafter used interchangeably and referred to as HTAs, are produced in cooperation with clinical experts in the field and based on documentation submitted by the manufacturer, patients can be involved if considered necessary (Proba samfunnsanalyse, 2021). The HTA should be completed within 180 days of commissioning, excluding days

spent awaiting documentation from the manufacturer (St. Meld 28 (2014-2015), 2015). The National Procurement services for Health Enterprises Ltd can engage in price negotiation with the manufacturer simultaneously as the HTA is produced, or following a negative decision in Decision Forum due to high price on the pharmaceutical (Proba samfunnsanalyse, 2021).

Following completion of the HTA, the HTA is subject to input from the manufacturer. Commissioning Forum then either approves the HTA and forwards to Decision Forum or return it to the body who performed the HTA for corrections (Nye Metoder, 2021a; Proba samfunnsanalyse, 2021). If the HTA is approved by Commissioning Forum, the HTA is then processed in Decision Forum. Decision Forum consists of the Chief Executive Officers of the Regional Health Authorities who prepares its recommendations on reimbursement based on the HTA and input from their medical professional staff (Prop. 55 L, 2019). There are several co-opted members to Decision Forum, one of them is a patient representative who is entitled to speak but has no weigh in the decision. Other co-opted members are NoMA, the Institute of Public Health, the Directorate of Health, and more. Decisions are based on the priority criteria and the methods fulfilment of these, quality of documentation, costs, and ethical consideration. The proposition on judicial regulation also states that there can be other and more important considerations than cost-efficiency that can be decisive in the decision on reimbursement (Prop. 55 L, 2019). Decisions by Decision Forum is either to reimburse the pharmaceutical, not reimburse, or other decisions such as ranking, disinvestment etc. depending. Following decision in Decision Forum, a positive decision on reimbursement will be followed by implementation through necessary adjustments in treatment guidelines and programs.

Appendix 2 – Table describing processing time by indication

All numbers are given as absolute days.

Legend:

* NoMA did not prioritize completion the HTA report as there were no incidences in Norway

Ŧ No decision had been made by 31.12.2021

₸ The dates stated by New Methods for completion of report and decision time does not add up, there has been a new decision in April 2022 which this report probaby is produced for, prior HTA reports was not found.

** Second decision on this indication

*** Third decision

**** Fourth decision

***** Fifth decision

Product name	Indication number	Time elapsed from MA to start of HTA	Time elapsed from MA to final decision	Time elapsed from Commissioning Forum to start of HTA	Time elapsed from start to completion of HTA	Self reported completion time of HTA	Self reported waiting time for supplement documentation	Time elapsed from completion of HTA to decision
Adcetris	1	551	851	71	176	176		124

Product name	Indication number	Time elapsed from MA to start of HTA	Time elapsed from MA to final decision	Time elapsed from Commissioning Forum to start of HTA	Time elapsed from start to completion of HTA	Self reported completion time of HTA	Self reported waiting time for supplement documentation	Time elapsed from completion of HTA to decision
Adcetris	3	1975	2216	179	196	97	39	45
Adcetris	2	1716	1926	130	164	164		46
Adcetris	5	2821	3105	213	217	171	40	67
Alofisel**	1	-64	339	423	238	164	74	165
Alprolix	1	1	214	-31	167	167		46
Arzerra	1	1415	1645	78	211	178		19
Arzerra	2	560	938	114	324	240	84	54
Bavencio	1	86	343	359	272	85	69	27
Besponsa	1	177	481	375	255	225	30(100)	49
BlenrepŦ	1	297	-	291	256	190	5	
Blincyto	1	-10	203	200	168	168		45
Blincyto	3	1781	2191	297	354	138	49	56
Brineura*	1	398	1609	434	1166	1158		45
Bronchitol	1	3184	3335	66	113	40	42	38
Cablivi	1	266	634	549	320	154	55	48
Crysvita	1	1107	581	-455	284	170	22	45
Darzalex	1	137	521	113	261	216	59	123
Darzalex	2	410	521	127	97	67	28	14
Darzalex	1	1505	1802	-115	262	221	0	35
Elzonris	1	357	165	857	-219	133	0	27
Enspryng	1	0	305	451	253	250	0	52
Epidyolex	1	307	739	667	380	268	32	52

Product name	Indication number	Time elapsed from MA to start of HTA	Time elapsed from MA to final decision	Time elapsed from Commissioning Forum to start of HTA	Time elapsed from start to completion of HTA	Self reported completion time of HTA	Self reported waiting time for supplement documentation	Time elapsed from completion of HTA to decision
Evrysdi	1	-4	297	-70	274	132	74	27
Farydak	1	788	1249	183	370	367	3	91
Gazyvaro	1	182	552	309	328	332		42
Gazyvaro	2	682	1067	39	361	361		24
Gazyvaro	3	1029	1291	78	209	184	25	53
Givlaari	1	134	574	106	402	303	21	38
Idelvion**	1	54	376	21	115	115	0	207
Imbruvica	1	140	419	358	206	179		73
Imbruvica	2	254	552	472	193	193		105
Imbruvica	4	1758		1778		133	49	
Isturisa	1	405	703	611	268	149	0	30
Jorveza	1	402	623	-11	153	151	0	68
Kaftrio₸	1	383	150	268	93	56	37	-326
Kymriah	1	-72	87	203	150	58	95	9
Kymriah	2	-51	397	161	344	344	164	104
Kyprolis	1	15	312	256	217	180	37	80
Kyprolis	2	397	641	190	198	176	22	46
Lamzede	1	17	269	77	217	204	13	35
Lartruvo	1	98	474	65	259	287	44	117
Ledaga	1	1218	1571	620	264	243	9	89
Lenvima**	1	-	1005	-	-	183		641
Libmeldy₸	1	168	-	220	334	320	0	

Product name	Indication number	Time elapsed from MA to start of HTA	Time elapsed from MA to final decision	Time elapsed from Commissioning Forum to start of HTA	Time elapsed from start to completion of HTA	Self reported completion time of HTA	Self reported waiting time for supplement documentation	Time elapsed from completion of HTA to decision
Luxturna**	1	70	886	892	372	247	59	444
Lynparza	1	73	307	74	181	178		53
MyaleptaŦ	1	1052	-	288	259	88	65	
Mylotarg	1	116	522	294	343	310	33	63
Namuscla	1	622	860	0	186	163	9	52
Ninlaro****	1	32	392	284	207	360	30	153
Onivyde***	1	-7	374	116	277	204	57	104
Palynzig	1	-193	759	444	428	133	45	80
PemazyreŦ	1	28	-	214	319	290	39	
Polivy	1	19	368	286	321	285	19	28
Poteligeo	1	676	1012	868	260	230	24	76
Prevymis	1	67	413	7	224	204	20	122
Qarziba	1	407	770	876	321	290	31	42
Ravicti	1	804	1005	51	124	123		77
Reblozyl	1	201	536	351	311	90	42	24
Rydapt	1	161	763	308	487	459	28	115
Rydapt	2	161	763	308	490	490		112
Scenesse	1	1057	1498	518	399	331	68	42
Soliris	4							
Soliris	2							
Soliris	1							
Spinraza***	1	31	510	123	101	101		378

Product name	Indication number	Time elapsed from MA to start of HTA	Time elapsed from MA to final decision	Time elapsed from Commissioning Forum to start of HTA	Time elapsed from start to completion of HTA	Self reported completion time of HTA	Self reported waiting time for supplement documentation	Time elapsed from completion of HTA to decision
Symkevi	1	51	810	32	725	341	123	34
Takhzyro	1	161	431	192	246	148	55	24
Translarna₮	1	671		583	453	102	40	
Vimizim	1	2433		514	278	328	0	
Trecondi	1	245	543	2383	328	228	0	20
Vyndaqel	1	-10	301	284	291	81	135	20
Vyxeos	1	-55	522	-59	553	412	91	24
Xermelo	1	242	1131	38	862	721	14	27
Xospata	1	21	535	39	451	269	70	63
Yescarta	1	615	978	862	304	165	30	59
Zejula**	2	36	1383	123	650	155	495	697
Zejula	3	670	921	-34	210	199	4	41
Zejula	4	4	277	91	228	186	0	45
Zolgensma	1	53	525	529	203	176	24	269
Zynteglo	1	167	544	197	359	196	0	18

Appendix 3

Appendix table 1 Quartiles of high estimated QALY gain and difference between NoMA and manufacturer.

Quartiles of estimated QALY gain	High estimates of QALY gain by NoMA	High estimates of QALY gain by manufacturer	Diff (NoMA-man)
0 %	0,037	0,045	-0,008
25 %	0,538	0,9	-0,362
50 %	1,105	1,935	-0,83
75 %	2,78	4,305	-1,525
100 %	12,6	18,8	-6,2

Appendix table 2 Quartiles of high estimated QALY gain and difference between NoMA and manufacturer.

Quartiles of estimated QALY gain	Low estimates of QALY gain by NoMA	Low estimates of QALY gain by manufacturer	Diff (NoMA-man)
0 %	0,037	0,045	-0,008
25 %	0,505	0,9	-0,395
50 %	1,065	1,885	-0,82
75 %	2,6625	3,925	-1,2625
100 %	12,6	18,8	-6,2

Appendix 4

Appendix table 3 Shapiro Wilk test for normality of incremental cost and incremental QALY gain

Shapiro-Wilk W test for normal data

Variable	Obs	W	V	z	Prob>z
ipc_low_noma	42	0.67792	13.220	5.449	0.00000
ipc_high_n~a	42	0.67679	13.266	5.456	0.00000
ipc_an_noma	42	0.67917	13.168	5.441	0.00000
ipc_low_man	42	0.69372	12.571	5.343	0.00000
ipc_high_man	42	0.68785	12.812	5.383	0.00000
ipc_an_man	40	0.70889	11.507	5.141	0.00000
qalylow_noma	50	0.71139	13.573	5.562	0.00000
qalyhigh_n~a	50	0.72117	13.113	5.489	0.00000
qaly_noma_an	50	0.71638	13.338	5.525	0.00000
qalylow_man	52	0.75190	12.035	5.318	0.00000
qalyhigh_man	52	0.76819	11.245	5.173	0.00000
qalygain_m~n	52	0.76110	11.588	5.237	0.00000

Appendix table 4 Mann-Whitney U test of the low estimates of incremental cost

```
. ranksum iclow, by(ic_NoMA1man0)

Two-sample Wilcoxon rank-sum (Mann–Whitney) test
```

ic_NoMA1man0	Obs	Rank sum	Expected
0	42	1743	1785
1	42	1827	1785
Combined	84	3570	3570

```
Unadjusted variance    12495.00
Adjustment for ties       -0.89
                       ---------
Adjusted variance      12494.11

H0: iclow(ic_NoM~0==0) = iclow(ic_NoM~0==1)
         z = -0.376
Prob > |z| = 0.7071
Exact prob = 0.7102
```

Appendix table 5 Mann-Whitney U test of the high estimates of incremental cost

```
. ranksum ichigh, by(ic_NoMA1man0)

Two-sample Wilcoxon rank-sum (Mann–Whitney) test
```

ic_NoMA1man0	Obs	Rank sum	Expected
0	42	1734	1785
1	42	1836	1785
Combined	84	3570	3570

```
Unadjusted variance    12495.00
Adjustment for ties       -0.89
                       ---------
Adjusted variance      12494.11

H0: ichigh(ic_NoM~0==0) = ichigh(ic_NoM~0==1)
         z = -0.456
Prob > |z| = 0.6482
Exact prob = 0.6515
```

Appendix table 6 Mann-Whitney U test of the mean estimates of incremental cost

```
. ranksum icmean, by(ic_NoMA1man0)

Two-sample Wilcoxon rank-sum (Mann–Whitney) test

ic_NoMA1man0 |       Obs    Rank sum    Expected
-------------+---------------------------------
           0 |        42        1740        1785
           1 |        42        1830        1785
-------------+---------------------------------
    Combined |        84        3570        3570

Unadjusted variance    12495.00
Adjustment for ties       -0.89
                     ----------
Adjusted variance      12494.11

H0: icmean(ic_NoM~0==0) = icmean(ic_NoM~0==1)
         z = -0.403
Prob > |z| = 0.6873
Exact prob = 0.6904
```

Appendix table 7 Mann-Whitney U test of the low estimates of incremental QALYs

```
. ranksum qalylow, by(qaly_NoMA1man0)

Two-sample Wilcoxon rank-sum (Mann–Whitney) test

qaly_NoMA1~0 |       Obs    Rank sum    Expected
-------------+---------------------------------
           0 |        52        3000        2678
           1 |        50        2253        2575
-------------+---------------------------------
    Combined |       102        5253        5253

Unadjusted variance    22316.67
Adjustment for ties       -2.27
                     ----------
Adjusted variance      22314.40

H0: qalylow(qaly_N~0==0) = qalylow(qaly_N~0==1)
         z =  2.156
Prob > |z| = 0.0311
Exact prob = 0.0308
```

Appendix table 8 Mann-Whitney U test of the high estimates of incremental QALYs

```
. ranksum qalyhigh, by(qaly_NoMA1man0)

Two-sample Wilcoxon rank-sum (Mann–Whitney) test

qaly_NoMA1~0 |       Obs    Rank sum    Expected
-------------+---------------------------------
           0 |        52      2990.5        2678
           1 |        50      2262.5        2575
-------------+---------------------------------
    Combined |       102        5253        5253

Unadjusted variance    22316.67
Adjustment for ties       -1.77
                     ----------
Adjusted variance      22314.90

H0: qalyhigh(qaly_N~0==0) = qalyhigh(qaly_N~0==1)
         z =  2.092
Prob > |z| = 0.0364
Exact prob = 0.0362
```

Appendix table 9 Mann-Whitney U test of the mean estimates of incremental QALYs

```
. ranksum qalymean, by(qaly_NoMA1man0)

Two-sample Wilcoxon rank-sum (Mann–Whitney) test

qaly_NoMA1~0 |      Obs    Rank sum    Expected
-------------+---------------------------------
           0 |       52        3004        2678
           1 |       50        2249        2575
-------------+---------------------------------
    Combined |      102        5253        5253

Unadjusted variance    22316.67
Adjustment for ties       -1.89
                     ----------
Adjusted variance      22314.77

H0: qalymean(qaly_N~0==0) = qalymean(qaly_N~0==1)
         z =  2.182
Prob > |z| = 0.0291
Exact prob = 0.0288
```

Appendix table 10 Chi2 and Fisher's exact test of dependence between reimbursement status and appraisal track

```
. tab reimb_nor appraisal, chi2 exact

           |        appraisal
 reimb_nor |         3          4 |     Total
-----------+----------------------+----------
         0 |        23          9 |        32
         1 |        36          8 |        44
-----------+----------------------+----------
     Total |        59         17 |        76

          Pearson chi2(1) =   1.0548   Pr = 0.304
           Fisher's exact =                 0.405
   1-sided Fisher's exact =                 0.226
```

Appendix table 11 Chi2 and Fisher's exact test of dependence between reimbursement status and use of comparator in clinical trial

```
. tab reimb_nor comp_trial, chi2 exact

           |       comp_trial
 reimb_nor |         0          1 |     Total
-----------+----------------------+----------
         0 |        12         20 |        32
         1 |         8         36 |        44
-----------+----------------------+----------
     Total |        20         56 |        76

          Pearson chi2(1) =   3.5656   Pr = 0.059
           Fisher's exact =                 0.070
   1-sided Fisher's exact =                 0.053
```

Appendix table 12 Two-sample test of proportions of reimbursement of orphan drugs before and after transferal of financial responsibility

```
. prtesti 63 1 63 .9516

Two-sample test of proportions                     x: Number of obs =       63
                                                   y: Number of obs =       63
------------------------------------------------------------------------------
             |       Mean   Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
           x |          1          0                            1           1
           y |     .9516   .0270383                     .8986059    1.004594
-------------+----------------------------------------------------------------
        diff |      .0484   .0270383                    -.0045941    .1013941
             |   under H0:     .02738     1.77   0.077
------------------------------------------------------------------------------
        diff = prop(x) - prop(y)                                  z =   1.7677
    H0: diff = 0

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(Z < z) = 0.9614         Pr(|Z| > |z|) = 0.0771          Pr(Z > z) = 0.0386
```

Appendix table 13 Two sample test of proportions on reimbursement decisions on orphan drugs before and after White paper on priority setting

```
Two-sample test of proportions                     x: Number of obs =       28
                                                   y: Number of obs =       44
------------------------------------------------------------------------------
             |       Mean   Std. err.      z    P>|z|     [90% conf. interval]
-------------+----------------------------------------------------------------
           x |       .714   .0853991                      .573531     .854469
           y |       .545   .0750719                     .4215177    .6684823
-------------+----------------------------------------------------------------
        diff |       .169   .1137049                    -.0180279    .3560279
             |   under H0:   .1178725     1.43   0.152
------------------------------------------------------------------------------
        diff = prop(x) - prop(y)                                  z =   1.4338
    H0: diff = 0

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(Z < z) = 0.9242         Pr(|Z| > |z|) = 0.1516          Pr(Z > z) = 0.0758
```

Appendix 5

All conditions which orphan drugs underwent HTA by NoMA with their respective shortfall estimates and reimbursement status

Product name	Condition	Absolute shortfall low estimates	Absolute shortfall high estimates	Reimbursement status in Norway
Adcetris	CD30 pos Hodgkins lymphoma	0	0	Reimbursed
Adcetris	systemic anaplastic large cell lymphoma (sALCL) non-Hodgkin lymphoma	0	0	Reimbursed
Adcetris	cutaneous T-cell lymphoma	0	0	Not reimbursed
Adcetris	Hodgkins lymphoma	21,8	21,8	Reimbursed
Adcetris	systemic anaplastic large cell lymphoma (sALCL)	13,3	13,3	Reimbursed
Alofisel	Rectal Fistula following Crohns disease	9,4	9,4	Reimbursed
Alprolix	Hemophilia B	3,3	3,3	Reimbursed
Arzerra	Chronic lymphotic leukemia	0	0	Not reimbursed
Arzerra	Untreated Chronic lymphotic leukemia	0	0	Reimbursed
Bavencio	Merkel cell carcinoma	8,4	8,4	Not reimbursed
Besponsa	Acute Lymphatic Leukemia	28,4	28,4	Reimbursed
Blenrep	multiple myeloma	0	0	Unknown
Blincyto	acute lymphoblastic leukaemia	0	0	Not reimbursed
Blincyto	acute lymphoblastic leukaemia	0	0	Reimbursed

Product name	Condition	Absolute shortfall low estimates	Absolute shortfall high estimates	Reimbursement status in Norway
Brineura	neuronal ceroid lipofuscinosis type 2	65	65	Not reimbursed
Bronchitol	cystic fibrosis in adults in addition to best standard of care	30	30	Reimbursed
Cablivi	acquired thrombotic thrombocytopenic purpura	1,5	2	Not reimbursed
Crysvita	X-linked hypophosphataemia	30	30	Reimbursed
Darzalex	multiple myeloma	0	0	Reimbursed
Darzalex	multiple myeloma	0	0	Reimbursed
Darzalex	Combination treatment for multiple myeloma	14	14	Not reimbursed
Elzonris	blastic plasmacytoid dendritic cell neoplasm	0	0	Not reimbursed
Enspryng	neuromyelitis optica spectrum disorders	9,2	9,2	Not reimbursed
Epidyolex	Dravet syndrome	34	49	Reimbursed
Epidyolex	Lennox-Gastaut syndrome	32	52	Reimbursed
Evrysdi	5q spinal muscular atrophy	0	0	Reimbursed
Farydak	multiple myeloma - new combination	7,65	7,65	Reimbursed
Gazyvaro	chronic lymphocytic leukaemia	6,5	6,5	Reimbursed
Gazyvaro	follicular lymphoma	12,1	12,1	Reimbursed
Gazyvaro	follicular lymphoma, 1.line	9,9	9,9	Reimbursed
Givlaari	Acute hepatic porphyria	0	0	Not reimbursed

Product name	Condition	Absolute shortfall low estimates	Absolute shortfall high estimates	Reimbursement status in Norway
Idelvion	Hemophilia B	3,3	3,3	Reimbursed
Imbruvica	chronic lymphocytic leukaemia	6,5	6,5	Reimbursed
Imbruvica	mantle cell lymphoma	11,82	11,82	Not reimbursed
Imbruvica	Waldenström's macroglobulinaemia (1)	0	0	Not reimbursed
Imbruvica	Waldenström's macroglobulinaemia (2)	0	0	Not reimbursed
Isturisa	Cushings syndrome	0	0	Not reimbursed
Jorveza	eosinophilic oesophagitis (1)	0	0	Reimbursed
Jorveza	eosinophilic oesophagitis (2)	0	0	Reimbursed
Kaftrio	cystic fibrosis (F/F mutation)	35,8	35,8	Not reimbursed
Kaftrio	cystic fibrosis (F/MF mutation)	35,8	35,8	Not reimbursed
Kaftrio	cystic fibrosis (F/G mutation)	35,8	35,8	Not reimbursed
Kaftrio	cystic fibrosis (F/RF mutation)	35,8	35,8	Not reimbursed
Kymriah	B-cell acute lymphoblastic leukaemia	51,16	51,16	Reimbursed
Kymriah	Diffuse large B-cell lymphoma	15,5	15,5	Not reimbursed
Kyprolis	multiple myeloma	0	0	Reimbursed
Kyprolis	multiple myeloma - combination	8,76	12,66	Reimbursed

Product name	Condition	Absolute shortfall low estimates	Absolute shortfall high estimates	Reimbursement status in Norway
Lamzede	mild to moderate alpha-mannosidosis	48,6	48,6	Not reimbursed
Lartruvo	advanced soft tissue sarcoma	17,5	17,5	Not reimbursed
Ledaga	malignant melanoma	0	0	Not reimbursed
Lenvima	differentiated thyroid carcinoma	14,51	14,93	Not reimbursed
Libmeldy	metachromatic leukodystrophy	62,7	69,2	Unknown
Luxturna	inherited retinal dystrophy with mutation in the RPE65 gene	28,2	28,2	Reimbursed
Lynparza	cancers of the ovaries	17,38	17,38	Reimbursed
Myalepta	lipodystrophy	35,1	35,1	
Mylotarg	acute myeloid leukaemia	9,5	9,5	Reimbursed
Namuscla	myotonia (muscle stiffness) in patients with non-dystrophic myotonic disorders	0	0	Reimbursed
Ninlaro	multiple myeloma	0	0	Reimbursed
Onivyde	metastatic adenocarcinoma of the pancreas	17,4	17,4	Not reimbursed
Palynzig	phenylketonuria	0	0	Not reimbursed
Pemazyre	cholangiocarcinoma	0	0	Unknown
Polivy	diffuse large B-cell lymphoma	15,5	15,5	Reimbursed
Poteligeo	mycosis fungoides and Sezary syndrome subgroup	0	0	Not reimbursed

Product name	Condition	Absolute shortfall low estimates	Absolute shortfall high estimates	Reimbursement status in Norway
Prevymis	prevent illness caused by cytomegalovirus	13,3	13,3	Reimbursed
Qarziba	neuroblastoma	42,7	42,7	Reimbursed
Ravicti	paroxysmal nocturnal haemoglobinuria or atypical haemolytic uraemic syndrome	0	0	Reimbursed
Reblozyl	anaemia	20	24	Not reimbursed
Rydapt	acute myeloid leukaemia	9,5	9,5	Reimbursed
Rydapt	aggressive systemic mastocytosis	0	0	Reimbursed
Scenesse	erythropoietic protoporphyria	11	11	Not reimbursed
Soliris	atypical haemolytic uraemic syndrome	0	0	Unknown
Soliris	Neuromyelitis optica spectrum disorder	0	0	Unknown
Soliris	myasthenia gravis	0	0	Unknown
Spinraza	5q spinal muscular atrophy (Type I)	71	71	Reimbursed
Spinraza	5q spinal muscular atrophy (Type II)	67	67	Reimbursed
Spinraza	5q spinal muscular atrophy (Type III)	47	47	Reimbursed
Symkevi	cystic fibrosis (F/F mutation)	30	30	Reimbursed
Symkevi	cystic fibrosis (F/RF mutation)	28	28	Reimbursed
Takhzyro	hereditary angioedema	0	0	Not reimbursed

Product name	Condition	Absolute shortfall low estimates	Absolute shortfall high estimates	Reimbursement status in Norway
Translarna	Duchenne muscular dystrophy	0	0	Unknown
Trecondi	Conditioning prior to bone marrow transplant	9	19	Reimbursed
Vimizim	mucopolysaccharidosis type IVA	0	0	Unknown
Vyndaqel	transthyretin amyloidosis	8,2	8,2	Not reimbursed
Vyxeos	acute myeloid leukaemia	9,5	9,5	Not reimbursed
Xermelo	severe diarrhoea associated with the condition carcinoid syndrome	1,3	1,3	Not reimbursed
Xospata	acute myeloid leukaemia	9,5	9,5	Reimbursed
Yescarta	Diffuse large B-cell lymphoma	15,5	15,5	Not reimbursed
Zejula	cancer in fallopian tubes or peritoneum	11,9	11,9	Reimbursed
Zejula	ovarian cancer (1)	14,96	14,96	Reimbursed
Zejula	ovarian cancer (2)	17,5	17,5	Reimbursed
Zolgensma	spinal muscular atrophy	71	71	Reimbursed
Zynteglo	beta thalassaemia	20,3	24	Not reimbursed