New priorities – different decisions?

How would the new prioritization guidelines proposed by the Norheim committee affect decision making when financing drugs in Norway?

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Abstract

Background: The set of prioritization criteria in the Norwegian health care is about to be changed again. This master thesis set forth to elaborate what would happen if some of the new proposed changes to prioritization suggested by the Norheim report replace the existing guidelines on decision-making in relation to the financing of drugs. Which types of drugs would or would not gain public reimbursement, and why?

Methods: By looking at economic evaluations and decisions for six drugs, I try to show trends and consequences that might come as a result for future decisions by following some of the concrete suggested changes in the Norheim report. I investigate proposed changes to discounting, severity and thresholds. The reports produced by NoMA are detailed and by also accessing the underlying material for the analysis, I were able to make quite precise changes to former economic evaluations.

Results: Based on the recalculation and reevaluation, I expected the recommendation of public financing of the drugs to change in one of the cases, and possibly change for two of the drugs, depending of interpretation and practical use of Norheim. Changing the discount rate from 4 % to 0 % for health effects reduced the ICER in all of the six cases. The analysis showed that when comparing the ranking of the six drugs in regards to severity, absolute shortfall was closer to health loss, than was proportional shortfall.

Conclusions: By these six cases, I believe that changing from existing prioritization criteria and operationalization to Norheim’s proposals could have some implications. Whether these implications are desirable or not, needs to be debated.
Foreword

I want to thank the Norwegian Medicines Agency (NoMA) for giving me the material needed to make the thesis possible and for being flexible with my working schedule. This has made it possible for me to work fulltime at NoMA while writing this thesis, which in turn has led to a somewhat slow but steady writing process. Big thanks to my supervisors Hans Olav Melberg and Morten Aaserud for having patience throughout this work process.

Vorrei anche ringraziare l’Università di Bologna per un semestre così incredibile. Un semestre che era un grande motivazione per finire questo Master. Imparavo cose importante per finire il tesi e cose interessante per fare economia della salute in un modo nuovo.

Before reading on you should know that:

- The goal of this thesis is not to evaluate the fairness or justice of the Norheim proposal but only to evaluate the potential effects/consequences if the proposals are adopted.
- The goal of this thesis is not to evaluate the fairness or justice of severity calculations but only to try to compare effects of the different methods used to calculate severity.
- In this thesis, I consider prioritization proposals from three different prioritization committees; Lønning I (1987), Lønning II (1997) and Norheim (2014). When I write about Norheim and Lønning, I consider the whole committee of workers behind the reports, not only the person bearing the same name as the report.
- In the process of writing this thesis, a committee led by Jon Magnussen delivered a report proposing new direction for severity in prioritization. The Magnussen rapport is not included in this thesis.
- There has been an ongoing debate in Norway about how to calculate and operationalize severity in the Norwegian health care setting. This thesis compares three different methods for calculating severity: Health loss over lifetime, absolute shortfall and proportional shortfall.
In June 2016, the government published a report on prioritization (Helse- og omsorgsdepartementet, 2016). This thesis is based on the reports by both Norheim (Norheim, 2014) and Magnussen (Magnussen, 2015) which discuss health loss over a lifetime and absolute shortfall respectively. The comparison of these two methods in the calculation of severity is therefore of particular relevance.
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Background

The challenges of prioritization in health is an important and relevant topic because:

- Health is one of the most important element for peoples welfare
- There is a limit to available resources which creates a need to prioritize
- There have been three committees in Norway proposing different ways to prioritize health (Lønning, 1987) (Lønning, 1997) (Norheim, 2014)
- The government has as of June 2016 proposed new guidelines for prioritization in the health care sector (Helse- og omsorgsdepartementet, 2016)

The debate has become accessible for everyone through media. In the media, these discussions often arise with the entry of new and usually more effective drugs, which are often very costly. The importance of prioritization, and doing it correctly, is also becoming clearer for more people. Introduction of new medicines for the treatment of cancer, often paint a very clear picture of what you get for your money. A clinical study gives more or less promising results of prolonged lifetime, and the drug price shows you the large costs. The willingness to pay for a month gained thus becomes visible which stimulates a debate whether to spend tax money on such investments. The debate also spills over into different sectors especially because of debates on the need to allocate more money to the health sector in order to be able to afford the budgetary constraints for the new treatments. However, no matter how much reallocation of funds from other sectors to the health sector is undertaken, the need for prioritization still prevails.

Additionally, in the unavoidable situation where time is a scarce resource, a discussion about whom to treat first will take place for example when budgetary allocation for a new treatment is available but labor resources are scarce. This will inevitably enhance the need for prioritization.
Introduction

The set of prioritization criteria in the Norwegian health care is about to be changed again. This master thesis set forth to elaborate what would happen if some of the new proposed changes to prioritization suggested by the Norheim report replace the existing guidelines on decision-making in relation to the financing of drugs. Which types of drugs would or would not gain public reimbursement, and why? These questions are important to answer before deciding on whether to discard the old criteria in favor of the new.

This thesis will start out by giving an overview of the proposals from the three different priority reports (Lønning I (1987), Lønning II (1997) and Norheim (2014), and discuss differences and similarities between them. This is followed by background information as regards public drug financing in Norway, as well as an overview of the methods, proposed changes in the Norheim report that will be investigated, and at which operationalization level.

The thesis will further give an outline of how I recalculated different health economic analysis and which results I found. I will go on to discuss the findings and try to draw some conclusions and possible implications of the findings.
Prioritizing health in Norway
The following section will give an overview of the three proposed prioritization guidelines in Norway. In 1987, Norway got a proposal for prioritization guidelines, which were later known as the "Lønning I Report" NOU 1987: 23 (Lønning, 1987). Five priority levels were proposed. Further proposals for prioritization criteria came in the 1990s when the Lønning Committee delivered "Priorities again" NOU 1997: 18, better known as Lønning II (Lønning, 1997). According to Lønning II the government should give priority to conditions with high severity where relevant treatments have substantial expected benefits and the costs are reasonable in relation to the treatments advantage. A proposal for the third prioritization guideline came in 2014 and was conducted by Norheim (Norheim, 2014).

Lønning I
In the discussion of the objectives, principles and guidelines for future prioritization processes within the Norwegian health care system, the Committee took a view based on public perceptions of values, which are considered to have broad consensus in the Norwegian society. They found that it seemed self-evident that general ideals such as justice, equality and freedom - also should be expressed in the health care service. They argued that it is generally accepted that the public feels committed to help disadvantaged and underprivileged members of society and that this commitment should be expressed explicitly in priority setting. The committee found itself responsible for considering two basic goals: To fight disease and to promote health. The committee drew attention to the fact that it is significantly easier to describe goals related to fighting disease than the goals related to the promotion of health.

Five dimensions of prioritization:

- Severity of the disease
- Equal opportunities regardless of geographical and social status and age
- Waiting time
- Health economic aspects
Whether the patient can be blamed for his/her own condition

The five dimensions for prioritization that were particularly highlighted in the mandate, were important and they all needed further analysis and clarification in order to be used properly:

- One of the five dimensions stood out as particularly decisive in the priority context: Disease severity.
- None of the five dimensions may be deleted from the list of relevant priority criteria. They all represent regards in which a good prioritization system must take into account.
- None of the five dimensions could, except for the disease severity in some situations, act as prioritization criterion without the support of one or more of the other criteria.

The efficiency criterion and severity criteria would together serve as the main criteria for prioritizing decisions within Norwegian health service in the future. Regarding the principle of equality, the committee argued that health services would be designed and organized in a way that everyone gets the same right to be as healthy as they can. This principle should be realized regardless of social, geographical and age inequalities.

The criterion that the committee's mandate calls health economic aspects was difficult. It was discussed to what extent economics should be taken into account when utilizing health resources. Health economics as a science was a new field and had not found its place and form. In that current situation when pressure on health resources was increasing, there was a need for a deeper understanding of health economic issues. The Committee emphasized in this context that it was important to distinguish between health economics and health productivity at the population level and the economic considerations on patient treatment at the individual level.

The fifth dimension raised the question of whether self-inflicted health problems should be given priority-consequences for the individual patient. The committee proposed that
individuals should not be punished for self-inflicted lifestyle choices. However, the development of the so-called "lifestyle diseases" must primarily be met through active information and preventive measures aimed at the entire population, not by moralistic reactions to individual patients who need help and care. The Commission nevertheless observed that there might be a need for clear attitudes in communication with the individual patient.

**Lønning II**

The most obvious effect of the Lønning I report relates to might be traced in the public debate. The proposed guidelines in Lønning I came to practical expression among others through the practice of the so-called waiting list regulations. Such use of the guidelines had not been contemplated in NOU 1987: 23, but was later proposed by the government. Waiting guarantee meant that the criteria "urgency" had gotten traction in the public debate about priorities. Overall, it is easy to conclude that the guidelines from 1987 had somewhat less effect than desired.

In keeping with its mandate, the committee of the Lønning II (Lønning, 1997), sought to continue the thinking of "Lønning I" (NOU 1987: 23). The committee discussed which criteria should be overriding in setting priorities in the Norwegian healthcare system. At this time, the principle that healthcare should be distributed fairly and that equality is an essential element was already generally accepted as a national objective. The Committee therefore proposed that similar cases, as much as possible, should be treated similarly; meaning that if one patient got an offer, it should be a goal to give all patients in the same situation the same offer. Conditions that characterized similar situations are listed below;

- severity of the condition,
- the measured benefit
- cost-effectiveness

Conditions with differences in these three criteria were legitimate grounds for discrimination. Criteria such as gender, ethnicity, previous harmful behavior, productivity,
lifestyle, sexual orientation and social status was under no circumstances to be considered relevant. The criteria of age, lifestyle that reduces the effectiveness of the intervention and certain social needs, were criteria that could be included in prioritization decisions at the clinical level.

Prioritization of health care and patients always depends on a weighing of relevant considerations. The Committee believed that the consideration of the severity and concern for the benefit of treatment were two basic priority principles. In addition, decisions should as far as possible be such that resources were used in the most effective manner.

Of the proposed prioritization criteria in NOU 1987: 23, the principle on severity was particularly emphasized by Lønning II. On the other hand, compared to the previous proposed guidelines, the Commission believed that the measure of benefits and cost effectiveness should be given greater weight.

Norheim

The Norheim committee was appointed by Royal Decree June 21st 2013. The committee was to evaluate how to prioritize Healthcare in Norway in the future and to document this in a report (Norheim, 2014). The committee was to consider existing prioritizing criteria such as the prioritization regulation (Helse- og omsorgsdepartementet, 2000) and the blue prescription regulation (Helse- og omsorgsdepartementet, 2007) and evaluate to what extent these still have value and to what extent these should apply in the health sector today. The committee was also to develop a new set of criteria should they find it necessary. The Norheim report concluded that clear goals are important for good prioritization. The objectives should be firmly rooted in the Norwegian welfare state values. Central among these are human dignity, solidarity, justice, equality, self-determination, freedom of choice, legal certainty, predictability and transparency.
An official report on prevention strategies for the health sector came out in 1991. It was titled "More good years of life for all" (Sosialdepartementet, 1991) It was a good title, but the report did not highlight the distribution of good years of life as much as it should have done. The Norheim Committee therefore proposes the objective "as many good years of life for all, fairly distributed" – as a primary objective for prioritization. This wording makes it clear that the aim is both to create as many good years of life for all and to ensure that these are fairly distributed. Both targets have the support of the welfare state values and more general objectives. Equality in the distribution of good years of life requires that the distribution of health benefits and health services be based on equal treatment, while emphasizing the good years of life that occur to the most disadvantaged.

Good prioritization requires that clear and well-founded priority criteria be used. Such criteria should be able to assist decision makers in ranking interventions. The committee believes that the currently existing priority criteria are good. The committee also believes that prioritizing in the Norwegian health service should be strengthened with new terminology and classification, some changes to the content and a greater degree of specification of what the criteria will entail in practice. The Commission proposes the following overall criteria:

- The health benefit criterion: an intervention’s priority increases with the expected health benefits (and other relevant welfare gain from the intervention)
- The resource criterion: an intervention’s priority increases the less resources it takes up
- The health-loss criterion: an intervention’s priority increases with the expected loss of health relative to what is the norm for the public.

The criteria should always be valued in relation to each other and should apply throughout the health service. This means that the criteria are meant to serve as a basis for prioritization in very different decision-making settings; from decision-makers at the national leadership level to health professionals in their clinical work. Even though there might be cases where there is no complete economic analysis, good documentation is essential.
The Health benefit criterion replaces the former utility criterion and part of the cost-effectiveness criterion. In the blue prescription scheme regulations, it is stated that a measure should show clinical effectiveness in the relevant clinical population and should be cost effective. The Health benefit criterion collects the effect part of both of these. Health benefit also appears to be less technical than utility and more directly relevant to the clinical level and for the population. The Health benefit criterion emphasizes health benefits in the form of good years of life, but makes it possible for other relevant welfare benefits to affect priorities. It places more emphasis on health outcomes and less emphasis on non-health outcomes such as sick payments.

The Resource criterion replaces parts of the cost effectiveness criterion. The new terminology makes the criteria appear less technical and emphasizes that many prioritizations, particularly at the clinical level, are about much more than what can be measured monetarily. Clinicians make decisions everyday where they consider the use of resources in the form of beds, equipment, and transport to the nearest hospital and of course time and attention.

The health loss criterion replaces the severity criterion. The health loss criterion intends to capture the most important distribution considerations: that health gains occurring to the disadvantaged should be given extra weight. The disadvantaged in this context are defined as those with the greatest decline in health measured from the norm - 80 good years of life for all. This reference value is set relatively high. Although life expectancy in Norway at birth is just over 80 years, the number of expected good years of life are about 67 years. The norm is set higher with the objective of more good years of life over a lifetime. The definition of loss of health makes it possible to calculate and compare the diagnostic groups with different prognosis for life cycle with the currently available treatment. For example, patients with a severe form of multiple sclerosis experience on average decline in health over a lifetime of about 40 good years of life. Atrial fibrillation gives an average loss of health of about ten good years of life (Norheim, 2014). Thus distribution considerations, based on the size of health loss, suggests that health gains for patients with multiple sclerosis should
be given a higher prioritization value than health gains from interventions to treat atrial fibrillation. A decline in health of ten good years of life is nevertheless of great importance. Measures aimed at atrial fibrillation could in many cases be given priority, but equally cost-effective measures for MS patients should be prioritized even higher.

The committee considered inclusion of four other proposals when choosing the criteria for prioritization. These include age, lack of alternative interventions, contributions to innovation, and rarity. The Commission concluded that these concerns were already well addressed/covered by the three main criteria.

The three main criteria can be used directly or with thresholds. Thresholds offer a reasonable measure of the relationship between use of resources and health benefits. This can be useful in situations where the decision maker is considering whether a given intervention should be implemented or not, or in instances where there is insufficient information about the interventions that are competing for the same resources. Instead of a single threshold, the Committee believes that there is a need for a set of thresholds, differentiated by loss of health. Thresholds should be based on the best estimate of the opportunity cost (alternative use of resources) of the measure that is being considered.
Drug politics and financing drugs in Norway

To investigate possible changes in drug financing to different prioritization proposals, it is necessary to investigate the proposed changes at the operationalization level. As we will see, Norheim proposes some changes at the operationalization level that might affect current decision-making. In the Methods part of this thesis, I will look at some of these changes, but first, we need to understand the system for financing drugs in Norway and how the decisions are made.

In 2004 – 2005 Norway got the overall political goals for drug politics. Medical and economically correct use of medicines is the Ministry of Health’s main objective for drug policy. Other goals are that the population should have access to safe and effective drugs regardless of ability to pay, and that Norway should pay the lowest price possible on drugs (Sosialkomiteen, 2004-2005). In 2015, Norway got a proposal for new political goals for drugs through a revision of the drug report (Legemiddelmeldingen) (Helse- og omsorgsdepartementet, 2015). The proposal received parliamentary approval in February 2016. The new political goals are:

- To ensure good quality on treatment with drugs
- To ensure the price on drugs is as low as possible
- To ensure equitable and rapid access to effective drugs
- To facilitate research and development.

The government debates that the treatment that is sufficient to achieve treatment goals for one patient, is not necessarily the newest and most expensive drug, and that it therefore is not given that it is best to use drugs with a marginal additional benefits that cost several times more than existing therapy. It is emphasized that the authorities as representative of the whole community and all patient groups must manage the total resources in the best possible way. Because it is the society that finances most of the costs, and not the individual players in the pharmaceutical market, it is the government's task to balance the needs, so that the goal of optimum health can be achieved for the entire population.
The political goals further state that the costs of medical treatment for serious illnesses should be refundable today. It will not however always be possible for the health care authorities to be in line with what the individuals themselves perceive as optimal treatment in all areas. The Ministry is of the view that this will become increasingly important, given that there is an increasing disconnect between what is medically treatable and what the society can afford. It is further stated that the pressure on the public financing of drug use may increase in line with the expected increase of the elderly population because older people are often on more medicines than other age groups.

It is emphasized that a proper prioritization of medicines will provide better health and improve health services to the population within a given budget. The cost of drug therapy must therefore be proportionate to the benefits, so that society does not waste resources that could have been more efficiently spent elsewhere. Key assumptions for promoting good priorities are to develop an efficient reimbursement system and to keep drug prices low.

The health care authorities are aware that there might be a gap between what is medically treatable and what is possible to finance. However, there is an understanding that the statutory arrangements should not make the gap bigger than what is understandable, reasonable and fair. It must be emphasized that undignified conditions cannot be accepted or tolerated.

**Preapproved reimbursement (The Blue Prescription System)**

In Norway, drugs can be approved for reimbursement through the blue prescription system. This is general reimbursement for drugs used in the primary care health sector. The blue prescription regulation got its name from the color of the prescription pad for publicly financed drugs. The blue prescription regulation is the foundation for the blue prescription system run by the Norwegian Medicines agency. The following is a description of the system and its purpose.
**Structure**

The structure of the system is based on applications of acceptance issued from the producer of the drug. The drug company bears the burden of proof of both clinical data and cost effectiveness data. Upon submission of the documentation, NoMA has 180 days to evaluate it and to make a decision whether to grant public reimbursement or not. To ease the workload and transparency for both the producer and NoMA, the department of pharmacoeconomics at NoMA has developed a set of guidelines to help the development process of the application (Statens legemiddelverk, 2012).

**Purpose**

NoMA evaluates the applications according to the blue prescription regulations that state that the drug must fulfil all of the following criteria to get general reimbursement:

- The drug must be effective in a relevant population
- The drug must be cost-effective
- The drug must be used to treat a severe disease
- The drug must be used to treat a condition that requires long term treatment

Three of the criteria are adopted from the Lønning I and II as means to exhaust good and just prioritization within publicly financed drugs in the primary health care sector. The criteria covering effect, cost-effectiveness and severity are all explicitly expressed in the Lønning reports. In addition, a criterion of treatment duration was added (Helse- og omsorgsdepartementet, 2007).

It is clear that the leading prioritization criteria are crucial for decision-making on whether to grant reimbursement for drugs in the primary health care sector. As such, changes to the operationalization of proposed prioritization criteria would have a major influence of the decision making process.
National System for introduction of new methods in the specialist health care sector (New Methods)

New Methods was established in 2013 and is a system for evaluating interventions and methods in the specialist health care sector. It was established based on the following reasons (Nye Metoder, 2016):

- Medical and health science methods change rapidly
- Varying or missing practice for evaluation of methods when introducing or removing interventions in the secondary health care
- Unsystematic decision-making by introducing and removing new interventions in the secondary health care differently between different geographical locations

New Methods aims to systematically evaluate and introduce new interventions to the secondary health care as a whole.

**Structure**

The meaning of Health technology is all interventions used to prevent, investigate, diagnose and treat diseases, including (re)habilitation and the organization of health services. A health technology assessment (HTA) is based on a systematic overview of research concerning efficiency and safety and an assessment of the consequences, usually in terms of health economics. HTAs is a tool for supporting appropriate prioritization and decisions making in order to ensure that introduction of new technologies are proven to be safe and effective. Based on documentation from producers, NoMA does Single technology assessments (STA) for drugs and assesses whether to give a recommendation to the regional health authorities (RHA) to finance the drug or not. The recommendations are based on three criteria stemming from the Law of patients- and user rights (Helse- og omsorgsdepartementet, 2001):

- Prognosis for the condition
- Effect of the technology
- Cost-effectiveness of the technology in the relevant indicated patient population.
Crucial in this evaluation is the economic evaluation of the drug carried out by NoMA. The final decision on whether to take up the new technology is made by a committee called Decision forum - which consists of the four general directors in the four regional health authorities. If necessary, LIS (National buyer of drugs) can do price negotiations in order to try to get lower prices and change potential negative decisions.

**Purpose**

The purpose of this system is to promote better and safer patient care. This is made possible through the systematic assessment of new health technologies with regard to efficiency, safety and consequences for patients, the health service and society in general. It will enable patients, health personnel and society in general to be certain that health technologies used in patient care are both safe and effective. The national system in its entirety will promote the rational use of resources within the health services.
Method

As discussed in the previous section, the operationalization and concrete suggestions in Norheim might change decisions on drug financing. In the rest of the thesis, I will look at actual decisions and try to recalculate these with some of the concrete suggestions and possible operationalization of the Norheim proposals. By looking at economic evaluations and decisions and implementing the proposed changes to these, I try to show trends and consequences that might come as a result for future cases by following some of the concrete suggested changes in the Norheim report. The reports produced by NoMA are detailed and by also accessing the underlying material for the analysis, I were able to make quite precise changes to former economic evaluations.

As previously described, there are differences between the old proposed prioritization criteria projected by Lønning I and Lønning II and the new ones projected by Norheim. To investigate the implications of these differences, we need to move to an operationalization level to better uncover relevant differences for drug prioritization. Norheim proposes three concrete elements that might be of great importance in decision making of drug financing. In this thesis, I will investigate the following:

- Discounting
- Severity
- Thresholds

The selected cases will be recalculated according to changes in these three elements, and the possible changes for the outcomes will be evaluated. The following section will elaborate these elements.

Note that although cost-effectiveness is an important foundation of decisions for public financing of drugs, factors such as uncertainty, available treatment and rareness of disease might also affect the decisions and recommendations.
Discounting
When assessing cost effectiveness, one makes use of economic models. These are capable of measuring the costs and effects of different drugs over time. The costs and effects of the different treatment options can occur at different points in time, and this is important. Time preference and time related uncertainty affect how we value costs and effects. To account for this, we make use of discounting, to calculate the present value of costs and effects. The formula for present value is:

\[ PV = \frac{C}{(1 + i)^n} \]

C is the cost or effect that must be discounted, \( i \) is the interest (or discounting rate) rate and \( n \) is the number of years away from the present. From the formula, we can see that the interest rate is of great importance for how much the present value is going to be. The sum of present value for both costs and effects are used directly in the cost effectiveness analysis. From this, it is obvious that the level of interest rate is of importance to the cost effectiveness and in turn the financing decision.

Norheim proposes changes to the discounting of future health effects. The standard, which is used today, stems from NoMA guidelines (Statens legemiddelverk, 2012) and The Directorate for Health’s guidelines (Helsedirektoratet, 2012) which prefers a discounting rate (interest rate) of 4 % for both costs and effects. Norheim argues to change the discounting rate for health effects from 4 % to 0 %. One argument is to increase priority for preventative interventions (Norheim, 2014). Another was that reducing the discounting rate to 0 % would make it easier to compare health gain with the size of health loss, which is undiscounted. In this thesis, the effect of using Norheim’s proposal on discounting was analyzed by changing the discount rate in the economic models from 4 % to 0 %.

Severity
Measuring the effect of handling severity is complicated. The existing practice of severity handling is not as explicit as the one proposed by Norheim. It might be reasonable to think
that severity is given more weight by Norheim compared to existing practice, but the level of informal and qualitative severity handling in the existing practice is of importance. As we will see, I try to formalize and quantify this practice. When calculating severity one makes use of QALYs, which is a concept introduced to economics in order to measure the effect of a new method by taking into account both changes in life expectancy and quality of life. Over time, QALY has evolved making use of standardized instruments such as EuroQol-5D, ShortForm 36 etc. These are instruments that describe certain abilities and states such as the ability to take care of oneself, level of pain and discomfort, level of anxiety etc. These questionnaires are given to patients to make them give a score on their condition. A QALY gain from treatment A is the increased number of QALY a patient is expected to get when receiving treatment A compared to the standard of care treatment B. Norheim discusses good years of life and suggests that this can be operationalized through QALYs (Norheim, 2014).

Health loss
Norheim introduced health loss over lifetime as an alternative to the traditional severity thinking. By looking at the previous health loss in addition to future loss for patients, Norheim introduces a new way of handling severity in Norway. Since the severity of different cases has great impact on which thresholds (maximum willingness to pay for health gain) are relevant when evaluating cost effectiveness, this new concept represents a change. The following section will elaborate how the health loss over lifetime and traditional severity measurements were calculated in the examples. The health care loss over lifetime was calculated in the following way (see figure 1):
Figure 1 Health loss

- The x-axis shows the life span in years for a group of patients, and the y-axis the number of QALYs for each year. The limit of 80 good years stems for the Norheim-report (Norheim, 2014).
- Area 1 represents the life the patient group on average has already lived prior to the treatment start at age A and the diagnosis the treatment was initiated for.
- A is the age at treatment start
- Area 2 represents the QALYs obtained with existing treatment.
- Line A to B represent the Life years obtained by existing treatment
- Area 3 is the health loss compared to the reference value of 80 good years (QALYs)

To calculate the health loss (Area 3), I multiplied the perfect health (Y axis: utility weight = 1) with the expected life age (x axis: 80) and then subtract the QALY gain from existing treatment (Area 2) and the cumulative QALYs for the persons (Area 1). Area 1 is found by calculating expected number of QALYs without disease. I used Swedish data who gives quality of life for different ages and Norwegian mortality rates given by Statistisk sentralbyrå. I considered this previous loss to constitute Norheim’s health loss over lifetime prior to treatment.
The health loss over lifetime might vary between individuals and the calculations are done on group level both when calculated prospectively and retro prospectively. The calculations are done without discounting.

**Comparing health loss over lifetime to absolute shortfall (AS) and proportional shortfall (PS)**

One of the requirements for general reimbursement is that the drug is used to treat a severe disease. In addition to being a requirement, severity is also tentatively used as means to decide governmental financing in that severity also plays a part in the total evaluation of the financing decision. It could be argued that a higher cost effectiveness ratio could be accepted for more severe diseases compared to less severe diseases. Severity has through the last years been tentatively calculated by NoMA as a foundation for a possible more formalized handling of severity. These calculations are done by looking only prospectively as opposed to the health loss over life time presented by Norheim, which also, considers the cumulative QALYs lost by the patient groups, prior to treatment. The forward-looking severity calculation was carried out in two different ways; proportional and absolute health loss or shortfall.
Figure 2 Absolute and relative shortfall

Figure 2 above is used to calculate Absolute shortfall (AS). Area 2 is QALY gain from existing treatment. This is found by extracting the QALY gain from the comparative treatment in the economic models. Area 2+3 is found by calculating expected number of QALYs without disease, at age A. I used Swedish data who gives quality of life for different ages and Norwegian mortality rates given by Statistisk sentralbyrå. Absolute shortfall (AS) – is the QALYs the patient group loses with existing treatment. This is shown as the blue area or 3 in the figure above.

Proportional shortfall (PS) – is calculated by considering the QALYs the patient group loses proportional to the QALYs without the disease. PS is shown in the figure above as the blue area divided by the blue + the beige area (3/(2+3)). PS is stated as a percentage.
Dividing severity into severity classes

Norheim has divided severity into different health loss classes (Norheim, 2014), see table 1.

<table>
<thead>
<tr>
<th>Health loss class</th>
<th>Health loss in the group</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Moderate (&lt;15 QALYs)</td>
<td>Alzheimers disease, acute coronary disease</td>
</tr>
<tr>
<td>2</td>
<td>Big (15-30 QALYs)</td>
<td>Diabetes type II, hepatitis C, chronic heart failure, advanced breast cancer</td>
</tr>
<tr>
<td>3</td>
<td>Very big (30-45 QALYs)</td>
<td>Multiple sclerosis, osteosarcoma</td>
</tr>
</tbody>
</table>

Table 1 Health loss classes

Severity has played a part in the economic evaluations carried out by NoMA. The explicit use of severity is not yet fully established, and a comparison between the existing handling of severity and Norheim’s proposed health loss, is therefore tricky. In an attempt to overcome some of these difficulties, I decided to divide results from existing severity calculations into three severity groups. This was done so that it would be easier to compare how the proposed health loss criteria will change how severity is evaluated. Absolute shortfall – has previously been calculated by NICE for the same diagnosis as exemplified in the Norheim report and are given in the table below. The calculations span from 3 QALYs as the lowest and 37 QALYs as the highest. Norheim divided health loss over lifetime into three categories and to ease the comparison it would be preferable to also divide AS into three categories. I used the span from 1 – 37 and divided by three (rounding up) and allowed the highest class to exist without an upper band.

<table>
<thead>
<tr>
<th>Absolute shortfall (QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity class 1</td>
</tr>
<tr>
<td>Severity class 2</td>
</tr>
<tr>
<td>Severity class 3</td>
</tr>
</tbody>
</table>

Table 2 Absolute shortfall classes
Relative shortfall – was also included in the report from NICE. As the relative shortfall is stated as a percentage, the scale theoretically spans from 0 % to 100 %. For simplicity, I divided the RS into three classes in order to ease comparison with the different groups as shown in Table 3.

<table>
<thead>
<tr>
<th>Proportional shortfall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity class 1</td>
</tr>
<tr>
<td>Severity class 2</td>
</tr>
<tr>
<td>Severity class 3</td>
</tr>
</tbody>
</table>

Table 3 Proportional shortfall classes

As seen from the NICE calculations in Table 4, the diagnosis represented are skewed to the right with respect to PS, in other words, towards 100 %. It could therefore be argued that the severity classes should be established considering this, meaning that other intervals could be more suitable. On the contrary, one could argue that the diagnosis presented by NICE are not representative, and that including other diagnosis would change the distribution of RS so that the presented severity classes would be fitting after all.

It needs to be stressed that my division of AS and RS into classes were done solely in an attempt to explore potential differences in considerations of severity. The division highly affect results from comparison with the proposed changes in severity consideration. Diagnosis might change severity class by considering previous health as proposed by Norheim, and this is dependent on the division of the severity classes.
<table>
<thead>
<tr>
<th>NICE technology appraisal</th>
<th>International classification of diseases (ICD)</th>
<th>Proportional</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column A</td>
<td>Average age Total QALYs for population not treated with new intervention (undiscounted)</td>
<td>QALYs expected without the disease</td>
<td>Proportional</td>
</tr>
<tr>
<td>Advanced breast cancer (TA 34)</td>
<td>C50 Malignant neoplasm of breast</td>
<td>68 0.57</td>
<td>21.2 97%</td>
</tr>
<tr>
<td>Metastatic melanoma (TA268)</td>
<td>C43 Malignant melanoma of skin</td>
<td>56 0.90</td>
<td>23.6 96%</td>
</tr>
<tr>
<td>Non small cell lung cancer (TA 192)</td>
<td>C34 Malignant neoplasm of bronchus and lung</td>
<td>60 1.00</td>
<td>20.5 95%</td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma (TA 178)</td>
<td>C64 Malignant neoplasm of kidney, except renal pelvis</td>
<td>60 1.24</td>
<td>20.5 94%</td>
</tr>
<tr>
<td>Metastatic colorectal cancer (TA212)</td>
<td>C19 Malignant neoplasm of colon</td>
<td>60 1.31</td>
<td>20.5 94%</td>
</tr>
<tr>
<td>Metastatic prostate cancer (TA259)</td>
<td>C51 [prostate cancer]</td>
<td>69 0.88</td>
<td>14.0 94%</td>
</tr>
<tr>
<td>Myelodysplasia (TA289)</td>
<td>C34 Other leukaemias of specified cell type</td>
<td>65 1.49</td>
<td>16.7 94%</td>
</tr>
<tr>
<td>Multiple myeloma 2nd subsequent relapse (TA 171)</td>
<td>C30 Multiple myeloma and multiple myeloma plasma cell neoplasms</td>
<td>62 1.72</td>
<td>18.9 91%</td>
</tr>
<tr>
<td>Stroke (TA 264)</td>
<td>C35 Multiple sclerosis</td>
<td>37 3.95</td>
<td>40.7 90%</td>
</tr>
<tr>
<td>Chronic myeloid leukemia (TA 241)</td>
<td>C02 Myeloid leukaemias</td>
<td>56 2.45</td>
<td>23.6 90%</td>
</tr>
<tr>
<td>Metastatic ovarian cancer (TA284)</td>
<td>C05 [malignant neoplasm of ovary]</td>
<td>59 3.40</td>
<td>21.2 84%</td>
</tr>
<tr>
<td>Alzheimer’s disease (TA 217)</td>
<td>C30 Alzheimer’s disease</td>
<td>77 1.56</td>
<td>8.7 82%</td>
</tr>
<tr>
<td>Severe rheumatoid arthritis (TA225)</td>
<td>M05 Other rheumatoid arthritis</td>
<td>50 5.38</td>
<td>28.6 81%</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis (TA292)</td>
<td>J44 Other interstitial pulmonary diseases</td>
<td>66 3.13</td>
<td>16.0 80%</td>
</tr>
<tr>
<td>Chronic heart failure (TA 287)</td>
<td>I50 Heart failure</td>
<td>60 4.16</td>
<td>20.5 80%</td>
</tr>
<tr>
<td>Psoriatic arthritis (TA220)</td>
<td>M06 Other rheumatoid arthritis</td>
<td>47 7.01</td>
<td>31.1 77%</td>
</tr>
<tr>
<td>Peritoneal mesothelioma (TA233)</td>
<td>J53 Gastrointestinal infections</td>
<td>68 3.71</td>
<td>14.6 75%</td>
</tr>
<tr>
<td>Diabetic macular oedema (TA301)</td>
<td>H35 Other retinal disorders</td>
<td>63 7.16</td>
<td>18.2 61%</td>
</tr>
<tr>
<td>Acute coronary syndromes (TA236)</td>
<td>I20 Angina pectoris</td>
<td>70 6.28</td>
<td>13.3 53%</td>
</tr>
<tr>
<td>Diabetes type II (TA288)</td>
<td>E11 Non-insulin-dependent diabetes mellitus</td>
<td>58 11.28</td>
<td>22.0 49%</td>
</tr>
<tr>
<td>Von Willebrand disease (TA 235)</td>
<td>D41 Malignant neoplasm of bone and articlar cartilage of limb</td>
<td>44 10.11</td>
<td>64.2 48%</td>
</tr>
<tr>
<td>Arrhythmias (TA275)</td>
<td>I48 Atrial fibrillation and flutter</td>
<td>74 5.70</td>
<td>10.6 46%</td>
</tr>
<tr>
<td>Hepatitis C (TA252)</td>
<td>B17 Other acute viral hepatitis</td>
<td>44 22.92</td>
<td>33.9 32%</td>
</tr>
<tr>
<td>Severe asthma (TA 278)</td>
<td>J45 Asthma</td>
<td>43 25.31</td>
<td>34.8 27%</td>
</tr>
<tr>
<td>VTE (treatment + sec prev) (TA261)</td>
<td>J52 Other venous embolism and thrombosis</td>
<td>50 20.58</td>
<td>23.0 13%</td>
</tr>
<tr>
<td>Average displaced treatment in NHS</td>
<td>disp</td>
<td></td>
<td>9%</td>
</tr>
</tbody>
</table>

Table 4 Proportional and absolute shortfall for different diagnosis
Thresholds
To evaluate a drug's cost-effectiveness, it is necessary to consider both costs and effects. One usually compares the cost and effects of the new treatment A with the existing treatment B. These differences are often presented as incremental cost-effectiveness ratio (ICER) given by the formula:

\[
\text{ICER} = \frac{(\text{Cost}_A - \text{Cost}_B)}{(\text{Effect}_A - \text{Effect}_B)}
\]

It is clear that both costs and effects will influence the ratio. To decide if a drug is cost-effective or not, the ICER is often evaluated according to thresholds and other prioritization criteria. Thresholds are of great importance when comparing existing practice with Norheim, as the thresholds are highly decisive when deciding public financing. Norheim suggests different thresholds for different severity classes as shown in the figure below. The idea that different classes of severity are assigned to different thresholds is an idea that is relatively easy to accept. The higher the severity, the greater the willingness to pay, ceteris paribus. What is more debated is the value of the different thresholds and how the thresholds might be linked, either stepwise or continuous. In today's evaluation there are no explicit thresholds. However, previous decisions might give a hint of the whereabouts of these thresholds. From decisions made public and discussed in media we can presume a range of 300 000 – 800 000 NOK/QALY as acceptable when deciding to finance a drug (Nilsen, 2015) (Bordvik, 2016).

Norheim proposes a step model where the limit varies with health loss relating to the intervention as shown in the figure below.

![Figure 3 Proposed thresholds in Norheim's proposal](image-url)
Selection of reports

Six applications were selected for reevaluation in an attempt to show trends and consequences of Norheim compared to recent decisions and to exemplify these. These were economic evaluations carried out by NoMA, and were suspected to illustrate certain points. The cases are shown in the table below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic area</th>
<th>Intuitive severity</th>
<th>ICER*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yervoy (ipilimumab)</td>
<td>Metastatic melanoma</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Tecfidera (dimethylfumarat)</td>
<td>MS</td>
<td>Very high</td>
<td>Low</td>
</tr>
<tr>
<td>Sovaldi (sofosbuvir)</td>
<td>Hepatitis C</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Jevtana (cabazitaksel)</td>
<td>Metastatic prostate</td>
<td>Cancer</td>
<td>High</td>
</tr>
<tr>
<td>Keytruda (pembrolizumab)</td>
<td>Metastatic melanoma</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Toctino (alitretinoin)</td>
<td>Exema</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

*ICER assessments in this column are based on NoMA’s recommendations in the actual cases

These six cases were expected to exemplify the following:

- Yervoy – a cancer drug with a high ICER and high severity according to AS/PS
- Tecfidera – a MS-drug with very high severity that had a low ICER. In the Norheim report MS has the greatest health loss of all presented diagnoses
- Sovaldi – a Hepatitis C drug to treat a chronic condition which is not cancer and has a presumed medium severity
- Jevtana – a drug to treat a cancer diagnosis which were, given the disease and the patient group, suspected to give different results when calculating AS, PS and health loss over lifetime
- Keytruda – a cancer drug with a high ICER which was expected to replace one of the other investigated drugs (Yervoy) in clinical practice
• Toctino – a drug to treat a chronically non-severe condition which does not affect overall survival

The goal was not to make a quantitative estimate of how many decisions would change over time. The distribution and compositions of cases assessed for public financing changes constantly and it would be difficult to forecast a change in number of cases based on reevaluation of a sample. The goal was rather to find examples for concrete consequences of operationalization of Norheim’s proposal, and try to evaluate how these consequences could be relevant for similar cases in the future.

Recalculating and reevaluating the reports
To investigate potential implications of the proposed operationalization in Norheim, I recalculated and reevaluated the six reports considering the three elements of Norheim’s proposal; discounting, severity and thresholds. Often, NoMA makes changes to the producer’s cost effectiveness analysis, based on difference in perception of which parameters better reflects clinical practice, evidence etc. To investigate the effect on changes, it was important to use then final edition of the economic model as it was used by NoMA to make a decision. The recalculation and reassessment was done in the following way:

• The health economic model which was used by NoMA to make a recommendation was collected for the six drugs. All models were carried out in Excel, and were available through NoMA’s systems. The models calculated the ICER based on cost effect input and were very complex in many cases. All models had alternative values for many of the parameters.

• The excel model was reset to NoMA’s base case. This was done by reading NoMA’s health economic reports discussing the NoMA’s recommendation. If there was doubt, the NoMA investigator who made the recommendation was consulted. In one of the cases, the drug manufacturer was consulted to reset the economic model to NoMA’s base case.

• The discount rate for effects in the model was changed from 4 % to 0 %. This change was easily executed in all six cases.
• Severity was then calculated as discussed above. The severity calculations made use of input collected from the Excel model reset to NoMA’s base case.

• The cases were placed into severity classes and corresponding Thresholds.

• The results were evaluated and discussed assessing the following:
  o The old ICERs calculated with 4% discounting rate and the new ICER calculated with 0% discounting.
  o The thresholds for corresponding severity classes.
  o A possible change in recommendation.
Results

Yervoy

Ipilimumab is an active ingredient, which was introduced with the brand name Yervoy to the Norwegian market in July 2011 (European Medicines Agency, 2011). Upon introduction, it was approved for the treatment of severe malignant melanoma for patients who progressed from standard treatment (dacarbazine (DTIC)). Ipilimumab was later approved for treatment of malignant melanoma in first line i.e. treatment of treatment-naïve patients.

Upon time of economic evaluation of ipilimumab, there was no formal system in place for these types of evaluation at the specialist health care level. New Methods was under construction, but it was formally not in place and the decision whether to finance Yervoy not, was to be made by the Directorate of Health. The economic evaluation was carried out by NoMA as a pilot. NoMA concluded in their report that the ICER for ipilimumab was barely 1 mill NOK/QALY, which they said, was higher than what is usually considered cost effective (Statens legemiddelverk, 2012). The Directorate of health concluded, partly based on this report and partly by considering other priority considerations, that ipilimumab was not to be financed by the Norwegian health care sector (Storvik, 2013). Nevertheless, Yervoy was later given to Norwegian patients through a phase IV clinical trial initiated by the government (NRK, 2013).

The economic evaluation report states that the scenario in which NoMA considered most likely, gives an ICER of 990 739 NOK/QALY. The report also stresses that this estimate is uncertain and that there exists several factors/assumptions in the analysis that are especially debatable.

Discounting

In the economic model, both costs and effects were discounted by a rate of 4 % according to NoMA’s guidelines of drug evaluation (Statens legemiddelverk, 2012). The economic model
demonstrating Yervoy’s cost effectiveness depended on a clinical trial reported by Hodi et al (Hodi, 2010). Since there was a difference in mortality numbers and the fact that some of the patients were still alive at the end of the study, the effect of both ipilimumab and its comparator was extrapolated for a total time of 10 years. Ipilimumab gained much of its additive effect from this extrapolation of effect in future years. Adjusting the discount rate of effects from 4 % to 0 %, keeping the discounting of costs to 4 %, changed the ICER from 990 739 to 845 506 NOK/QALY. This is expected since adjusting the discount rate for effect increases the present value of the effect.

**Severity**

The health loss of the patient group indicated for treatment at the point of economic evaluation was calculated as described in the Methods section.

<table>
<thead>
<tr>
<th>Yervoy (ipilimumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
</tr>
<tr>
<td>QALYs rest of life with standard treatment</td>
</tr>
<tr>
<td>QALYs in life pre treatment start</td>
</tr>
<tr>
<td><strong>Health loss over life time</strong></td>
</tr>
</tbody>
</table>

*Table 6 Health loss for Yervoy*

As seen from the table the patient cohort is relatively young, as one also would expect in a disease as malignant melanoma (Statens legemiddelverk, 2012). The QALY obtained from existing treatment is also relatively small, and this stems from the fact that there was no effective treatment of malignant melanoma prior to Yervoy. In fact, in the economic evaluation, Yervoy was compared to best supportive care (BSC). The QALYs acquired in life prior to treatment is, as regards to the calculations, assumed not to be influenced by the diagnosis. This is of course debatable, since some patients may experience a reduction in quality of life. However, this reduction is hard to estimate and may vary amongst patients. In case of a reduction in quality of life prior to treatment, the estimate of health loss will be too
low, and adjusting for this might move the treatment to a higher severity class. Calculations for absolute and proportional shortfall are given in the table below.

<table>
<thead>
<tr>
<th>Yervoy (ipilimumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
</tr>
<tr>
<td>QALYs existing treatment</td>
</tr>
<tr>
<td>QALE without disease</td>
</tr>
<tr>
<td><strong>Severity calculation AS (QALYs)</strong></td>
</tr>
<tr>
<td><strong>Severity calculation PS</strong></td>
</tr>
</tbody>
</table>

*Table 7 Absolute and proportional shortfall for Yervoy*

**Thresholds**

As regards health loss, it is assumed that patients indicated for this treatment will fall in Norheim’s class 3, Very Large Health Loss. As seen from the Norheim report, class 3 constitutes health loss of 30 – 45. Treatment with Yervoy is therefore just barely in class 3. The Norheim report gives the thresholds 750 000 – 1 000 000 for drugs with indications constituting a patient population of class 3.

**Overall evaluation**

Although Yervoy was given to Norwegian patients through the phase IV study, the general recommendation from the Directorate of Health based on cost effectiveness and severity, was that Yervoy was not considered a cost effective treatment option. Since this master thesis considers possible implications of operationalization of proposed prioritization guidelines in Norheim, the negative recommendation from NoMA is the interesting factor. With an ICER of 990 739 and the existing implicit thresholds at the time, NoMA concluded that the cost effectiveness of Yervoy was above what is usually considered cost effective treatment in Norwegian practice (Statens legemiddelverk, 2012). The severity of the disease was not discussed in detail although it was consensus that malignant melanoma is a grave and life threatening disease. Even when considering this it was found that the ICER was above of what normally was considered cost effective.
Calculations for absolute and proportional shortfall puts malignant melanoma in severity class 2 and 3 respectively. Compared to absolute shortfall, the new guidelines classify malignant melanoma as a more severe disease, and hence the threshold increases.

Adjusting the discounting rate reduces the ICER of almost 150 000 and the new threshold spans from below and above the new ICER. However, since the health loss was barely classified as class 3, it might be reasonable to argue that the treatment would have to make use of the lower scale of the proposed threshold range of 750 000 NOK – 1 000 000 NOK. Given this, it might be likely that Yervoy would not have gotten a positive recommendation with the new guidelines. On the other hand, since the ICER would be inside the span, one could argue that it would be easier for the decision makers to argue for financing the drug considering additional prioritizing criteria. Given that this is a hospital drug NoMA would not decide in this case, but would hand the recommendation to the Decision forum, where factors besides severity and cost effectiveness is considered.

Given a reduction in ICER of 150 000 (due to zero discounting of health effects) and the discussion above, it is uncertain what destiny Yervoy would have faced with the new guidelines as regards publicly financing. However, it is more likely that with the new guidelines, such a decision would be positive.
**Tecfidera**

Tecfidera contains dimetylfumarate, which is used in treatment of relapsing remitting multiple sclerosis (RRMS). The drug was ordered for single technology assessment by New Methods and an economic evaluation was carried out by NoMA spring 2014 (Statens legemiddelverk, 2014). In August 2014, the Decision forum decided that Tecfidera should be financed for use at Norwegian Hospitals. This decision was based on NoMA’s evaluation which stated that Tecfidera was considered a cost-effective treatment compared to Copaxone (glatrimeracetat) with an ICER of 84 926 NOK/QALY.

**Discounting**

The main effect of Tecfidera is slowing the patients’ disease development measured by movement through EDSS states, and postponing movement to serious EDSS states. Hence, some of the effect of Tecfidera occurs in the future, as the patient experience a less severe disease development when treated with Tecfidera. With this in mind, one would expect the ICER to decrease when changing the health effects discount rate from 4 % to 0 %. Such a change is also seen as implementing 0 % discount rate moves the ICER from 84 926 to 56 001. The change is not big. This might be because the incremental QALY gain of Tecfidera is relatively small.

**Severity**

RRMS is the diagnosis classified by Norheim as the most severe of the diagnosis included in their examples, and the health loss is stated to be extensively higher than for the second severe diagnosis (Norheim, 2014). In the model, the mean patient starting age is 37.8 as RRMS strikes quite young patients. The table below shows that existing treatment in RRMS produces 6.99 QALYs.
The calculations result in a health loss of 38.91, which places the diagnosis well into Norheim’s health loss class 3. Calculations of absolute shortfall and proportional shortfall give values of 27.31 and 80% respectively which place the diagnosis in health loss class 3 from both perspectives.

**Thresholds**

Concerning health loss and the class of severity, it is assumed that patients with RRMS will fall into class 3, Very Large Health Loss (Norheim, 2014). The Norheim report gives the thresholds 750 000 – 1 000 000 for drugs with indications constituting a patient population of class 3.

**Overall evaluation**

Tecfidera was decided financed by the Decision forum late summer 2014, and is today available for Norwegian patients. By the possible operationalization of Norheim it would be
likely that Tecfidera would get public financing even with a higher price, as adjusting the discounting rate would lead to a lower ICER. The health loss is assumed to be in class 3, which is the same as when calculating severity by AS and PS.

This reevaluation shows that when adjusting for possible operationalization of the proposed guidelines by Norheim, Tecfidera would still be recommended for public financing by NoMA even with a higher price than today.
Sovaldi

NoMA carried out a cost effectiveness evaluation of Sovaldi, which contains sofosbuvir, in 2015 (Statens legemiddelverk, 2015). The drug is used to treat Hepatitis C, and was the first in a group of new treatments for hepatitis C that was introduced in Norway in spring 2015. The economic evaluation distinguished between different genotypes of the disease, different interventions and comparators and different age groups. NoMA did a cost effectiveness evaluation of several other new drugs for treatment of hepatitis C too, and some of those were compared directly to Sovaldi. However, in this analysis I look at Sovaldi for treatment of hepatitis C with genotype 1. The ICER was estimated to be 109 333 NOK/QALY.

Discounting

The effect of Sovaldi is postponing major events and time to death. I therefore expected that discounting only costs would have a big effect on the cost effectiveness. That is also what is found when looking at the new ICER - with no discounting of health effects - which is 48 398 NOK/QALY.

Severity

The health loss becomes 19,18 that is inside Norheim’s health loss class 2. See table 10. This corresponds with the health loss stated in the Norheim report (Norheim, 2014).

<table>
<thead>
<tr>
<th>Sovaldi (sofosbuvir)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
</tr>
<tr>
<td>QALYs rest of life with standard treatment</td>
</tr>
<tr>
<td>QALYs in life pre treatment start</td>
</tr>
<tr>
<td><strong>Health loss over life time</strong></td>
</tr>
</tbody>
</table>

*Table 10 Health loss for Sovaldi*
Calculating AS gives 7.6 and a PS of 23%. It is important to notice that this calculation might have some limitations. These calculations have only considered the condition hepatitis C, but untreated hepatitis C might lead to severe conditions. Including risk for these conditions might give higher numbers when calculating severity by all three methods. I did not have data to support such a calculation and interpretation of results from severity calculation in this particular case must be done with care.

**Thresholds**

In relation to health loss and the class of severity, it is assumed that patients with hepatitis C will fall into class 2 according to health loss and 1 according to both AS and PS calculations. The Norheim report gives the thresholds 500 000 – 750 000 for class 2.

**Overall evaluation**

Sovaldi was considered cost effective by NoMA for genotype 1 with the ICER 109 333 (Statens legemiddelverk, 2015). By severity calculations, Hepatitis C would fall into either severity class 1 according to AS and PS, and by the health loss calculations in class 2. Using undiscounted effects gives a considerable lower ICER.

It would be safe to assume that Sovaldi would still be recommended for public financing by NoMA when using the proposed changes in Norheim, even if introduced with a higher price.
**Jevtana**

Jevtana, which contains cabazitaxel, is an alternative treatment for metastatic castration resistant prostate cancer (CRPC). The Norwegian Medicines agency assessed the statistical, medical and health economical documentation provided by Sanofi for treatment of second-line metastatic castration resistant prostate cancer with Jevtana in Norway (Statens legemiddelverk, 2013). The report was published in 2013 with a recommendation that with an ICER of about 1,26 mill NOK Jevtana was not cost effective compared to prednisolone. During the fall 2013, the Decision forum decided that Jevtana was not to be financed in the Norwegian specialist care.

**Discounting**

Main finding of the TROPIC study (cabazitaxel + prednisolone versus mitoxantrone + prednisolone) was an increased median overall survival of 2.4 months, from 12.7 months to 15.1 months (Oudard, 2011). Jevtana significantly improved total and progression free survival, time to prostate-specific antigen (PSA) progression and decreased tumor growth rate (Statens legemiddelverk, 2013). Hence changing the discount rate for effects would result in a better ICER because future effects are given more value. This is also the case as the ICER drops to about 1,13 mill NOK/QALY when not discounting health effects.

**Severity**

As regards class of health loss, it is assumed that patients indicated for this treatment will fall in Norheim’s class 2 as seen in the table below. The Norheim report states that class 2 constitutes a health loss of 15 – 30 and is classified as a big loss (Norheim, 2014).

The severity calculations gives an absolute shortfall of 11.48 which falls into AS severity class 1. Calculating the proportional shortfall on the other hand, places the patients indicated for this treatment into class 3. As seen in this example, the absolute and the relative shortfall gives very different severity estimates, ending in two extreme opposite directions, with the health loss in the middle.
### Jevtana (cabazitaxel)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>68</td>
</tr>
<tr>
<td>QALYs rest of life with standard treatment</td>
<td>0,83</td>
</tr>
<tr>
<td>Qalys in life pre treatment start</td>
<td>56,03</td>
</tr>
<tr>
<td><strong>Health loss over life time</strong></td>
<td><strong>23,14</strong></td>
</tr>
</tbody>
</table>

*Table 12 Health loss for Jevtana*

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>68</td>
</tr>
<tr>
<td>QALYs existing treatment</td>
<td>0,83</td>
</tr>
<tr>
<td>QALE without disease</td>
<td>12,31</td>
</tr>
<tr>
<td><strong>Severity calculation AS (QALYs)</strong></td>
<td><strong>11,48</strong></td>
</tr>
<tr>
<td><strong>Severity calculation PS</strong></td>
<td><strong>93 %</strong></td>
</tr>
</tbody>
</table>

*Table 13 Absolute and proportional shortfall for Jevtana*

**Thresholds**

Each of the three different severity calculations gives different results, which would lead to the use of different thresholds. The health loss calculations gives the threshold 500 000 - 750 000 for drugs with indications constituting a patient population of class 2.

**Overall evaluation**

Older patients with prostate cancer exemplifies that different ways of calculating severity can give different results. However, in this case, not even the proportional shortfall would give a threshold high enough to recommend the drug as cost effective. Not even when health is not discounted. However, not discounting and using the proportional shortfall would give an ICER somewhat closer to the threshold (Nilsen, 2015), which could help establishing a foundation for price negotiation.
**Keytruda**

Keytruda (pembrolizumab) is a PD-1-blocker that is used to treat malignant melanoma. Keytruda was proven better than Yervoy (ipilimumab) in a clinical study (Robert, 2015). The treatment was thus expected to replace Yervoy in the treatment of patients with malignant melanoma, and the cost effectiveness assessment conducted by NoMA compared these two treatments (Statens legemiddelverk, 2015). NoMA concluded in their report that Keytruda was not considered a cost effective treatment with the list price and had an ICER of almost 900 000 NOK/QALY. After price negotiations, Keytruda was found cost-effective with a confidential discount. In the following, we will ignore the process with price negotiation and treat this example as a negative recommendation from NoMA.

**Discounting**

Keytruda showed significant improvement in progression free and overall survival compared to Yervoy (Robert, 2015) and it was expected that reducing the discounting rate from 4 to 0 % would reduce the ICER significantly. That is also the case as the ICER dropped from almost 900 000 NOK/QALY to below 700 000 NOK/QALY.

**Severity**

Since Keytruda is indicated for the same patient group as Yervoy. As seen from the table the patient cohort for Keytruda is somewhat older than the one in Yervoy. The QALY gain from existing treatment is also different for Keytruda because Yervoy was the standard care at point of evaluation. These factors together make the health loss for Keytruda patients somewhat smaller than for Yervoy patients. In fact, as it moves from above 30 to below 30, the health loss class changes from class 3 to class 2. The table below gives the calculation for health loss. The absolute and the proportional shortfall are also reduced from Yervoy to Keytruda, but these changes are not sufficient to change the severity class. It is important to notice that the different age in the different economic models contributes to the changes of severity calculations from Yervoy to Keytruda.
Thresholds

Since the health loss class is changed from 3 for Yervoy to 2 for Keytruda – for the same disease, the threshold is changed from 750 000 – 1 000 000 to 500 000 – 750 000. However, a health loss of about 26 is in the higher end of the threshold, meaning it would be reasonable to expect a threshold closer to 750 000. It can also be argued to use discretion while evaluating similar drugs for similar conditions.

Overall evaluation

There is a change in the severity assessment of Keytruda compared to the assessment of Yervoy, based on two elements:

- The patients in the evaluation of Keytruda is slightly older than in the evaluation of Yervoy
- Since Yervoy was standard of care upon time for evaluation for Keytruda, the QALY gain from existing treatment was better when evaluating Keytruda

Despite of a reduction in severity, the reduction in ICER as result of the change in discount rate might change the decision of Keytruda (with the list price) as a cost effective alternative to Yervoy. The drop in ICER of about 200 000 NOK/QALY places Keytruda well below the upper threshold given for severity class 2. In conclusion, the new guidelines from Norheim would change the recommendation of Keytruda with its approved maximum price.
Toctino

Toctino (alitretinoin) is indicated for treatment of severe chronic hand eczema. NoMA evaluated the cost-effectiveness analysis done by the producer and found that Toctino resulted in an QALY gain of 0,05 and an incremental cost of 25 000 compared to placebo (Statens legemiddelverk, 2014). This resulted in an ICER of 475 000 NOK/QALY.

Discounting

The economic model on which the ICER was calculated was recreated (with an ICER of approximately 479 000 NOK/QALY) and the model was run without discounting health benefits as recommended by Norheim. This resulted in an ICER of approximately 470 000 NOK/QALY, which gives a reduction of about 9 000. This small reduction was expected given that the health gain was small. In addition, the model was run for only 2 years, which means that considerable future health gains were not expected.

Severity

Due to the indication, we expected a lower severity in this case compared to the others. This is also what I found. The mean age of the patients in the evaluation was 48, and the health loss and severity calculations are given in the tables below.

<table>
<thead>
<tr>
<th>Patient age</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>QALYs rest of life with standard treatment</td>
<td>22,3</td>
</tr>
<tr>
<td>QALYs in life pre treatment start</td>
<td>42,33</td>
</tr>
<tr>
<td><strong>Health loss over life time</strong></td>
<td><strong>15,37</strong></td>
</tr>
</tbody>
</table>

*Table 16 Health loss for Toctino*
### Toctino (alitretinoin)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>48</td>
</tr>
<tr>
<td>QALYs existing treatment</td>
<td>22.3</td>
</tr>
<tr>
<td>QALE without disease</td>
<td>26</td>
</tr>
<tr>
<td><strong>Severity calculation AS (QALYs)</strong></td>
<td><strong>3.7</strong></td>
</tr>
<tr>
<td><strong>Severity calculation PS</strong></td>
<td><strong>14 %</strong></td>
</tr>
</tbody>
</table>

*Table 17 Absolute and proportional shortfall*

The calculations gave a health loss of barely 15 QALYs. This is the lowest of the six cases that I evaluated. The absolute shortfall was calculated to 3.7 and the proportional shortfall was 14%. These are all low numbers and indicate that by all three calculations, chronic hand eczema is not a very severe condition. The severity calculations for the AS and PS ended up in severity class 1, which is the lowest for these categories. The calculations of health loss were above 15, which places it in class 2 for health loss.

**Thresholds**

According to Norheim, the calculations for health loss lead to a threshold of 500 000 – 750 000. This is higher than the expected threshold for this kind of condition using today’s thresholds (Nilsen, 2015).

**Overall evaluation**

It seems that using the Norheim criteria would still give a positive decision. It also seems that this decision would more likely be positive with Norheim, than it is today, since the ICER is slightly reduced and severity calculations seems to have increased the threshold. This could imply that Toctino would get a positive recommendation even with a higher price. Adjusting for base loss (to be evaluated in the discussion) might be of importance in this case. As we move into the discussion section, I will elaborate this further.
Discussion
This section discusses and summarizes main findings and implications that might be expected from the proposed changes by Norheim. I will also discuss strengths and weaknesses by this analysis.

Discounting
Throughout the six cases, I found some similarities. Changing the discounting rate from 4% to 0% decreases the ICER in all of the six cases. From the implications of discounting this is expected. As seen from the Table 18, the change in ICER due to change in discounting varies between the cases from 9 000 to 200 000 NOK/QALY.

It seems that for cases with drugs resulting in a considerable health gain in the future, the reduction in discounting rate is expected to give greater changes in ICER, see table 18. This is seen in the cases of Sovaldi, Keytruda, Yervoy and Jevtana. This change alone will give more priority to drugs giving bigger QALY gains especially if these are expected in the future. A high discount rate will severely deprioritize preventative treatment diminishing the QALY gain year by year and changing the discounting rate from 4 % to 0 % will up-prioritize preventative treatment. This hypothesis is supported by the finding of Sovaldi which is a treatment to prevent severe consequences of Hepatitis C. Changing the discounting rate led to a decrease in ICER of 56 %, which is the highest reduction (in percent) in ICER due to discounting.

It is important to notice that the time horizon for the model is important for the effect the discount rate has on the ICER. Changing the discount rate will obviously give little impact on models that run for a shorter time, as there will be fewer future health effects included. The case of Toctino illustrates this. The Toctino model was run for only 2 years, which includes only 1 year of discounted health effects. This was therefore further investigated by running the model with a 10 year perspective, including a bigger share of future health gains. The ICER when running the model with a 10 year perspective, and both costs and effects are
discounted by 4\%, was then 237 886 NOK/QALY. Running the model again with 10 year perspective and discounting only costs with 4\% gave an ICER of 217 134 NOK/QALY. The change in ICER is now bigger (about 9\%) and this is believed to stem from the delta effect in the 10 year perspective which is now 0.12. However, the reduction in ICER is still small which supports the theory that as long as the delta effect is small, it does not matter much if you discount effects or not, as there is not much to discount.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Delta effect in QALYs w/disc. 4%</th>
<th>Delta effect in QALYs w/disc. 0%</th>
<th>Absolute increase in delta effect in QALYs (0% disc. rate – 4% disc. rate)</th>
<th>% increase in delta effect</th>
<th>ICER w/disc. 4%</th>
<th>ICER w/disc. 0%</th>
<th>Absolute reduction in ICER</th>
<th>% reduction in ICER</th>
<th>Time horizon in years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yervoy</td>
<td>0,75</td>
<td>0,88</td>
<td>0,13</td>
<td>17%</td>
<td>990 739</td>
<td>845 506</td>
<td>145 233</td>
<td>15%</td>
<td>10</td>
</tr>
<tr>
<td>Tecfidera</td>
<td>0,179</td>
<td>0,271</td>
<td>0,092</td>
<td>51%</td>
<td>84 926</td>
<td>56 001</td>
<td>28 925</td>
<td>34%</td>
<td>20</td>
</tr>
<tr>
<td>Sovaldi</td>
<td>0,57</td>
<td>1,29</td>
<td>0,72</td>
<td>126%</td>
<td>109 333</td>
<td>48 398</td>
<td>60 935</td>
<td>56%</td>
<td>60</td>
</tr>
<tr>
<td>Jevtana</td>
<td>0,222</td>
<td>0,241</td>
<td>0,019</td>
<td>9%</td>
<td>1 226 000</td>
<td>1 133 000</td>
<td>93 000</td>
<td>8%</td>
<td>5</td>
</tr>
<tr>
<td>Keytruda</td>
<td>0,731</td>
<td>0,952</td>
<td>0,221</td>
<td>30%</td>
<td>900 000</td>
<td>700 000</td>
<td>200 000</td>
<td>22%</td>
<td>20</td>
</tr>
<tr>
<td>Tocitno</td>
<td>0,0521</td>
<td>0,0531</td>
<td>0,001</td>
<td>2%</td>
<td>479 000</td>
<td>470 000</td>
<td>9 000</td>
<td>2%</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 18 Effects of changed discounting rate on effect and ICER
This finding support a theory that Norheim’s proposed change in discount rate favours drugs that give a considerable QALY gain over those who give just a slight QALY improvement. This might be relevant for the evaluation for drugs, which are “patent prolonging”. One example is a new formulation “once daily” instead of “twice daily”. Another example is a new insulin which is acting longer than the existing ones, resulting in reduced injection frequency and fewer hypoglycaemic events and in sum leading to an overall QALY gain of barely 0,005. Such a QALY improvement will gain little from a reduction in discount rate, as seen in the case of Toctino. Therefore, ceteris paribus, one can argue that this change proposed by Norheim, given fixed budgets, favours interventions with a big QALY gain, over drugs with a small one, and make the market for drugs with marginal QALY gain more difficult. Whether this is a desirable change depends on the point of view. From the industry point of view, this relatively reduces the willingness to pay for “patent prolonging” adjustments and thus the prices for these drugs. From the payers point of view, this might be desirable as it is a means to cost control for “patent prolonging” drugs which in many cases gives little new to the patient.

**Severity**

Another factor that might change with the Norheim proposals is the severity calculations.

Table 19 gives an overview of the different severity calculations.

<table>
<thead>
<tr>
<th>Absolute values</th>
<th>Age</th>
<th>Absolute shortfall</th>
<th>Propotional shortfall</th>
<th>Health loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yervoy (cancer)</td>
<td>56</td>
<td>19,78</td>
<td>97 %</td>
<td>30,52</td>
</tr>
<tr>
<td>Tecfidera (MS)</td>
<td>38</td>
<td>27,31</td>
<td>80 %</td>
<td>38,91</td>
</tr>
<tr>
<td>Sovaldi (Hep C)</td>
<td>40</td>
<td>7,6</td>
<td>23 %</td>
<td>19,18</td>
</tr>
<tr>
<td>Jevtana (cancer)</td>
<td>68</td>
<td>11,48</td>
<td>93 %</td>
<td>23,14</td>
</tr>
<tr>
<td>Keytruda (cancer)</td>
<td>60</td>
<td>15,464</td>
<td>88 %</td>
<td>25,824</td>
</tr>
<tr>
<td>Toctino (exema)</td>
<td>48</td>
<td>3,7</td>
<td>14 %</td>
<td>15,37</td>
</tr>
</tbody>
</table>

*Table 19 Comparison of severity calculations*

From the table we see that Tecfidera, which is used to treat Multiple Sclerosis, results in the highest health loss over lifetime. The three cancer drugs (metastatic) Yervoy, Keytruda and Jevtana follows, and in the bottom we find Sovaldi and Toctino. This trend is consistent with the AS calculations. The calculations of PS paint a different picture. By these calculations, the
three cancer drugs Yervoy, Jevtana and Keytruda are most severe with Tecfidera following a bit behind. At the bottom, find Sovaldi and Toctino.

Table 20 gives an overview of the six cases and associated severity classes. Overall, compared to AS, health loss over lifetime, places the indications in higher severity classes. According to health loss, both Tecfidera and Yervoy is in severity class 3. These diagnoses affect younger patients. Jevtana, which has the highest mean age of the six examples, is in severity class 2. One can argue that Norheim might prioritize younger patients with chronic diseases that have experienced a big loss, such as e.g. MS (Tecfidera). On the other hand, the age of the patient might affect the severity placement according to health loss and give lower priority to older patients such as e.g. prostatic cancer (Jevtana).

<table>
<thead>
<tr>
<th>Severity classes</th>
<th>Age</th>
<th>Absolute shortfall</th>
<th>Propotional shortfall</th>
<th>Health loss</th>
<th>HL vs AS</th>
<th>HL vs PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yervoy (cancer)</td>
<td>56</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tecfidera (MS)</td>
<td>38</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sovaldi (Hep C)</td>
<td>40</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Jevtana (cancer)</td>
<td>68</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>Keytruda (cancer)</td>
<td>60</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>Toctino (exema)</td>
<td>48</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 20 Comparison of severity classes

While interpreting results from Table 20, keep in mind that the severity classes for AS and PS are constructed by the author for this purpose. It might be more informative to investigate the ranking of the different drugs by severity, see Table 21.

<table>
<thead>
<tr>
<th>Health loss</th>
<th>Absolute shortfall</th>
<th>Propotional shortfall</th>
<th>Health loss</th>
<th>HL vs AS</th>
<th>HL vs PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecfidera (MS)</td>
<td>38,91</td>
<td>27,31</td>
<td>97 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yervoy (cancer)</td>
<td>30,52</td>
<td>19,78</td>
<td>93 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keytruda (cancer)</td>
<td>25,824</td>
<td>15,464</td>
<td>88 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jevtana (cancer)</td>
<td>23,14</td>
<td>11,48</td>
<td>80 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sovaldi (Hep C)</td>
<td>19,18</td>
<td>7,6</td>
<td>23 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toctino (exema)</td>
<td>15,37</td>
<td>3,7</td>
<td>14 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 21 Comparison of ranking according to severity calculations

The ranking confirms the findings that Health loss and AS calculations lead to the same ranking, while PS has fewer similarities with the two others. This might be partly because both AS and Health loss are absolute measures, while PS is a relative measure.
Thresholds and recommendations

The most interesting factor may be the recommendations concerning public financing. Table 22 states the existing recommendations compared to possible recommendations of Norheim’s proposed operationalization.

<table>
<thead>
<tr>
<th>Overall evaluation</th>
<th>Existing recommendation</th>
<th>Possible recommendation (based on Norheim)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yervoy</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Tecfidera</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Sovaldi</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Jevtana</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Keytruda</td>
<td>Negative</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Toctino</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 22 Possible changes in recommendation of public financing of the cases

As shown in the table a change of public financing recommendation is expected in one of the cases; Keytruda. For this drug, all of the severity calculations gave high numbers, and the reduction in discounting was considerable. For the other cases, the ICER was reduced due to the change in discount rate but considering the thresholds, it was not sufficient to change the recommendation. It is however difficult to predict how the use of the thresholds and the severity classes would be in practice. In the case of Yervoy for example, the ICER with changed discount rate is under 850 000 NOK/QALY, and the severity of the underlying condition equals a health loss of over 30 QALYs which places it in the third threshold group 750 000 – 1 000 000 NOK/QALY. As discussed earlier it might be plausible to think that the Decision forum would say no, given that the severity is just above 30 QALYs, and thus at the lower end of the interval. However, this is just an assumption. It might also be the case that as long as the severity equals a threshold class, the Decision forum would make use of the entire threshold class and exercise discretion when forming a decision. In such a case, there might also be a change of decision for Yervoy – from negative to positive.
It is likely that Tecfidera and Sovaldi would still get a positive recommendation while Jevtana would still get a negative one.

**Adjusting for base-loss**

One of the critiques Norheim has faced is the argument that in calculating health Loss over lifetime, Norheim has not considered the standard health loss that all individuals face. Just by living a normal healthy life, you will lose about 10 QALYS (Magnussen, 2015). This challenges the use of health loss as the Norheim thresholds do not seem to have an adjustment for this.

To evaluate the possible impact of adjusting for base-loss, I did additional analysis where I considered a base-loss of 10 QALYs occurring to all people. This loss was implemented by changing the severity classes by Norheim, and by making use of the health loss class 0, as shown in the table below. The health loss class of 0 was constructed by the author of this thesis for this purpose as this is not thoroughly discussed by Norheim (Norheim, 2014).

<table>
<thead>
<tr>
<th>Health loss class</th>
<th>Health loss in the group</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not specified &lt;10</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Moderat (10-25) QALYs</td>
<td>Alzheimers disease, acute coronary disease</td>
</tr>
<tr>
<td>2</td>
<td>Big (25-40 QALYs)</td>
<td>Diabetes type II, hepatitis C, chronic heart failure,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>advanced breast cancer</td>
</tr>
<tr>
<td>3</td>
<td>Very big (40&lt; QALYs)</td>
<td>Multiple sclerosis, osteosarcoma</td>
</tr>
</tbody>
</table>

*Table 23 Health loss classes adjusted for base loss*

The calculated health loss for associated condition was used as before. As a result, the same condition was considered less severe when adjusting for base-loss, and the thresholds for the same severity was adjusted down. I further evaluated how this would affect possible
recommendations. As I used the same calculations, only the thresholds have changed. The results are shown in the table below.

<table>
<thead>
<tr>
<th>Overall evaluation</th>
<th>Existing recommendation</th>
<th>Possible recommendation</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yervoy</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Tecfidera</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Sovaldi</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Jevtana</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Keytruda</td>
<td>Negative</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Toctino</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 24 Possible changes of recommendation for public financing adjusted for base loss, dichotomously

The cases remain unchanged from before the adjustment of the base loss. Only for Keytruda would we expect a change in recommendation, as we did before the adjustment of the base loss. However, this evaluation was done by considering the thresholds dichotomously. By considering the position of the drug inside the different threshold classes, we would get a different result as shown in the table below.

<table>
<thead>
<tr>
<th>Overall evaluation</th>
<th>Existing recommendation</th>
<th>Possible recommendation</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yervoy</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Tecfidera</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Sovaldi</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Jevtana</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Keytruda</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Toctino</td>
<td>Positive</td>
<td>Negative</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 25 Possible changes of recommendation of public financing adjusted for base loss, continuous

Keytruda seem to be given the same recommendation when adjusting for base loss. Keytruda had a health loss of 26,14, barely placing it in health loss class 2 which when adjusting for base loss spans from 25 – 40. With and ICER of about 700 000 NOK/QALY and a threshold for class 2 spanning from 500 000 NOK/QALY to 750 000 NOK/QALY could be considered too high an ICER to be recommended. Toctino on the other hand is on the lower half of health loss class 1, which has a span from 10 – 25. With a threshold span from 250 000 to 500 000, the ICER for Toctino which was almost 500 000, could be deemed too high to be recommended, and we would get a change in recommendations based on Norheim.
Adjusting for base loss seems to change approximately the same number of cases as when not adjusting for base loss. The adjustment reduces the likelihood of a drug to be placed inside a threshold class with a higher threshold, and this could in turn affect drug-pricing policies. Considering the classes continuously results in an unchanged negative recommendation for Keytruda and a change from positive to negative recommendation for Toctino. It seems that adjusting for base loss balances some of the effects of the reduces ICERs due to 0 discounting rate of effects.

**Strengths of this thesis**

- This analysis makes use of real cases and has accessed the models and the entire documentation underlying the making of the decisions for the cases, which made it possible to consider a wide range of implications and considerations.
- The analysis was supervised by a member of the Norheim committee who assisted in interpreting the ideas and suggestions proposed by Norheim.
- The analysis had access to a wide range of cases to exemplify different effects.

**Weaknesses of this analysis**

- The analysis had to make some assumptions, which affect the results. The construction of severity classes for AS and PS retrospective of former decisions in the example cases is particularly important.
- The calculation of health loss had to be simplified, and the health loss taking place pre-treatment was not adequately considered. This might have led to an underestimation of severity when calculating the health loss.
- Some important implications of Norheim report may not have been discovered in this thesis due to reports selected for analysis.
- The analysis compares actual recommendations/decisions to possible recommendations/decisions which necessary introduces uncertainty.
Conclusion

By considering the decision for public financing for six drugs, this master thesis has shed light on possible implications of introducing the new prioritization criteria recommended by the Norheim committee. I investigated the possible operationalization of Norheim considering possible changes in discounting, severity and thresholds. I recalculation and reevaluated cost effectiveness and severity for six drugs to illustrate possible implications. Changing the discount rate from 4 % to 0 % for health effects reduced the ICER in all of the six cases. In some cases, where the QALY gain was big, the reduction in ICER was considerable. I argued that the size of the QALY gain, to which extent the treatment was preventative and time horizon of the economic model were particularly important for the effect on the ICER change. I further argued that this change might lead to higher drug prices and higher priority to preventative interventions as well as lower prioritization of treatments with small QALY gain e.g. “patent prolonging” drugs. The existing practice of severity handling is not as explicit as the one proposed by Norheim and comparison was challenging. However, the analysis showed that when comparing the ranking of the six drugs in regards to severity, absolute shortfall was closer to health loss, than was proportional shortfall.

Based on the recalculation and reevaluation, I expected the recommendation of public financing of the drugs to change in one of the cases, and possibly change for two of the drugs, depending of interpretation and practical use of Norheim. Adjusting for base loss (that happens to all patients in general during lifetime) seems to results in minor changes. The adjustment reduces the likelihood of a drug inside a class with a higher threshold, and this could in turn affect drug-pricing policies.

By these six cases, I believe that changing from existing prioritization criteria and operationalization to Norheim’s proposals could have some implications. Whether these implications are desirable or not, needs to be debated.
Referanser


