TANDVÅRDS- OCH
LÄKEMEDELSFÖRMÅNSVERKET

Calculation and payment

Continued study on evaluation methods and payment models for new medicines, such as ATMPs, and precision medicine

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Preface

Patients should have access to medicines that are effective and add value. But not at any price. TLV as an authority and society must be able to meet the challenges that come with the introduction of advanced – and expensive – therapies.
To do so, we need to develop our methods for health economic evaluation. We also believe that there is a need to rethink how medicines are paid for through approaches such as the development of payment models. Well-functioning price dynamics for medicines over their entire life cycle are important. We therefore believe that if priority is to be given to one type of medicine from a resource perspective, proposals on how to set higher cost-effectiveness requirements for other types of medicines need to be set in parallel.

TLV is continuously working to develop methods and approaches, including through the development of practices in our decisions and cases. In the government mandate on precision medicine and ATMPs that TLV reported on a year ago, we drew a number of conclusions about what we see as the main challenges. We also made suggestions on how the work should be taken forward. In the work presented in this report, TLV has taken some further steps forward: we have deepened some of the analyses and made a number of concrete suggestions on how to move forward. We have also explored how we as an authority can contribute to the development of payment models.

We hope and believe that the work outlined in this report will contribute to equitable access to medicines across the country and efficient use of our common resources to ensure that we get the most health for our tax money. TLV looks forward to taking this work forward – in continued collaboration with other actors.

Stockholm, April 2022

Agneta Karlsson, Director-
General of TLV

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Summary

The introduction of new types of technologies in healthcare means that the authorities and other actors responsible for the wise use of society's common resources need to continually develop their methods. How can we obtain an accurate picture of the health gains and costs generated by new technologies? How do we pay in a way that shares the risks between companies and payers in a fair way and thus makes treatments available to patients – even in situations where companies and payers have different views on the benefits of the medicine?

In this report, the Dental and Pharmaceutical Benefits Agency (TLV) reports on the work done in the context of a government commissioned project to develop methods for health economic evaluations of precision medicine and payment models for advanced therapy medicinal products (ATMPs). In this work, TLV has continued to investigate and analyse some of the proposals made by the Agency in a previous report, *How should we assess and pay? Health-economic assessments and payment models for precision medicine and ATMPs*, from April 2021.

Health economic evaluation of precision medicine poses some new challenges, but is fundamentally no different from evaluations of many other types of treatments for which we have limited knowledge of the medicine's efficacy. Many of the analyses and conclusions in this work can therefore be applied to many types of medicines, both for clinical and reimbursed medicines. However, for ATMPs, which are in-patient medicines administered in hospitals, a number of specific issues are raised. ATMPs are often a one-off treatment. If the entire payment is made at the time of treatment and the price charged by the company is based on a very long-lasting effect – which is often uncertain – the payer's risk is high. The risk is significantly higher than for continuous drug treatments. Some of the analyses in this work are therefore based on the challenges that are particularly pronounced for ATMPs.

The report is divided into four main parts, which are summarised below.

Part 1: Uncertainties: quantification, reporting, approach and payment

Quantifying, reporting and relating to uncertainties are key elements of all health economic evaluations, regardless of the type of medicine being evaluated.

Although the way uncertainties are described does not in itself reduce the uncertainty in a health economic evaluation, clear description can increase understanding of the parameters and assumptions underlying TLV's decisions, and thus provide a better basis for decision-making. TLV has begun an internal review of how it can more clearly quantify and report on the uncertainties in a health economic evaluation – not only for ATMPs and precision medicine, but for all types of medicines that TLV evaluates.

TLV has continued to investigate a question raised in the previous report – is there a case for differentiating the level of uncertainty accepted for a medicine to be reimbursed or recommended, based on the magnitude of the health gain lost by delaying treatment? Waiting to use the medicine until better evidence is available may be a strategy for the decision-maker to reduce uncertainty. However, the impact of delaying treatment differs for different conditions and treatments. TLV finds it reasonable to differentiate the degree of accepted uncertainty. For two medicines targeting two different but equally severe diseases where the cost per health gain is judged to be the same, there may be reasons to make different decisions – to accept greater (or less) uncertainty when the long-term consequence of withholding treatment is large (or small). The balance between uncertainty and loss of health gain in practical application needs to be developed in the context of TLV's management.

The greatest challenge in health economic evaluation of ATMPs is to deal with the uncertainties about the long-term effect. In the previous report, a proposal was made to apply a method where the calculation of cost per QALY (ICER) in the base case reflects that there are probabilities for different outcomes. The method involves weighting QALYs gained and costs at different durations of effect, with the weights being the probability of the effect persisting. In this report, TLV concludes that the probability-weighted ICER method may be particularly appropriate for ATMPs, where the duration of the effect is even more critical to cost-effectiveness compared to continuously administered medicines. An advantage of the method is that the ICER will then reflect that there is no evidence for actual duration of effect and that different outcomes are possible. The disadvantage of the method is that an assumption has to be made about what the annual probability of the effect disappearing is, and whether it increases or decreases over time. TLV therefore also sees a need to increase understanding of the duration of effect for ATMPs and how it may differ between different medicines with different underlying technologies, and believes that such development work is appropriate to undertake as part of a new government mandate. If the probability weighting method proves to be appropriate, it could also be applied to other medicines, where relevant, and also include other types of outcomes than duration of effect.

Outcome-based payment models can reduce the risk that the payment for a medicine is too high in relation to the benefit that the treatment provides when used in clinical practice. By reducing payer risk, these payment models can therefore be part of the solution in making ATMPs accessible to patients. In this report, we show how this risk reduction can be made visible using the probability-weighted ICER method.

TLV has begun development of a simulation tool that can be used by different stakeholders to gain a better understanding of the impact of different types of outcome-based payment models. In a first version, the tool is based on simplified, hypothetical conditions and aims to illustrate the main mechanisms. TLV aims to continue developing the tool for

use in more complex situations and to serve as a support in assessements of actual medicines. The first version of the simulation tool is available on the TLV website.

Part 2: Opportunities to support the development and use of new payment models

TLV has analysed the ways in which the Agency can and should support the development and use of outcome-based payment models for in-patient medicines, in particular ATMPs. The study was based on the Agency's mandate to conduct health economic assessments of in-patient medicines and other regulatory frameworks.

TLV finds that, in the context of the health economic assessments, the Agency could develop proposals for payment models by, inter alia, identifying and proposing urgent components to be addressed in such a model. Such a process includes an evaluation of how the negotiating parties' proposed payment model addresses the key uncertainties and how it affects cost-effectiveness, as well as an evaluation of proposed outcome measures and the possibility of monitoring them. If relevant to the specific case, TLV should also be able to suggest how the current payment models could be adjusted to be more appropriate in terms of achieving sufficient risk reduction. In some situations, the initial proposal for the appropriate payment model may also be essentially developed by TLV. A prerequisite for the above is that there is a mutual interest between the contracting parties to negotiate on a possible payment model.

TLV's assessment is that it is questionable whether the development of payment models and other contractual terms is part of TLV's current mandate to perform health economic assessments of in-patient medicines. TLV therefore proposes an amendment to the instructions for the Dental and Pharmaceutical Benefits Agency [förordningen (2007:1206) med instruktion för Tandvårds- och läkemedelsförmånsverket] to clarify that, for in-patient medicines, TLV may evaluate and develop proposals for payment models that can form the basis for a contract between regions and companies and also develop drafts of such contracts. A consequential amendment to the Public Access to Information and Secrecy Regulation (2009:641) [offentlighets- och sekretessförordningen (2009:641)] is therefore also needed so that confidentiality also applies to this new information.

Part 3: Whether the total usage of a medicine should influence the cost accepted

TLV considers it imperative to investigate how the total usage of a medicine should affect how high of a cost should be accepted. Normally, sales volume, sales value or budgetary impact do not affect the price accepted by TLV. However, in a small number of decisions, TLV has taken into account the fact that a medicine is targeted at a rare condition and has accepted a higher ICER than normal, in part because of the small number of patients. Is it reasonable to expand the application? Although not limited to ATMPs and precision medicine, the question is raised here because the patient groups concerned are often small and the companies are asking high prices for their medicines.

An examination of this issue should not be limited to medicines with small expected sales volumes, but should also address the question of whether it is reasonable to simultaneously set

higher cost-effectiveness requirements for high-selling medicines – to require greater and better proven health gains per krona paid for them.

Part 4: Taking into account the impact of a disease and a treatment on the quality of life of informal caregivers'

To date, TLV has not considered the impact of a new treatment on informal caregivers' quality of life, in its decisions. In this work, we have analysed this issue and concluded that in some situations it may be justified to consider this impact – for example, when the patient's condition leads to a very significant impact on the caregivers' daily life and situation and when there is evidence that reliably shows that the drug treatment can lead to an improvement in the health-related quality of life for the caregivers'.

However, there are methodological challenges around how to calculate impact and there are often gaps in the data and evidence. There are also doubts as to whether the impact that taking caregivers' into account has on the allocation of healthcare resources is compatible with the ethics platform of healthcare. However, TLV finds that it is compatible in cases where the impact on caregivers' is very significant. As a next step, TLV intends to continue reviewing methods for calculating the impact on the quality of life of family members and to develop criteria for when this impact should be taken into account.

In conclusion

Patients should have access to medicines that are effective and add value – regardless of the technology on which the medicine is based or the patient groups the product targets, and regardless of where in the country the patient lives. At the same time, this must be made possible without overcharging society and without crowding out other publicly-funded services. TLV therefore sees a need for continued ongoing development of health economic evaluation methodologies and outcome-based payment models – in order to meet the challenges posed by the introduction of new treatments – and suggests in the report a number of areas for further investigation. Collaboration with other actors in the field, such as regions, patient representatives and the pharmaceutical industry, is crucial for a good outcome. TLV looks forward to working further to find forms of collaboration that both enable equitable access to medicines across the country and efficient use of our shared resources.

Terms and definitions

Opportunity cost – the alternative use of a resource that is lost by choosing a particular course of action.

ATMP – advanced therapy medicinal products, or advanced therapies, include gene therapies, somatic cell therapies and tissue-engineered products.

Payment model – in this report, the term is used for a situation in which the payment is not a constant amount per pack, but may vary depending on the patient, indication, purchased volume, health outcome or other parameter. See also *outcome-based payment model*.

ICER (*Incremental Cost Effectiveness Ratio)* – see *Cost per QALY gained*

In-patient medicine – Medicine administered to the patient in a hospital or other healthcare facility.

Cost per QALY gained – a measure that relates the difference in cost between two treatment options to the difference in health (measured in terms of quality-adjusted life years, QALYs). This measure is also referred to as *ICER*, *Incremental Cost Effectiveness Ratio*.

Quality Adjusted Life Year (QALY) – a measure of health that captures both lifespan and health-related quality of life.

Sensitivity analysis – analysis carried out to see how different parameters, or changed scenarios, affect the outcome of a health economic calculation.

Pharmaceutical benefit – a medicine included in the pharmaceutical benefit scheme is reimbursed and included in the high-cost protection scheme, which limits how much a patient has to pay for their medicines.

Precision medicine – defined in this report as diagnostics, treatment and prevention based on the individual patient's molecular profile. For medicines and other therapies, TLV usually refers to precision medicine as a treatment where a molecular test controls the choice of treatment.

Real World Data (RWD) – data generated in clinical practice in the context of use. “Real World Evidence” (RWE) refers to the conclusions that can be drawn by analysing RWD.

Reimbursed – included in the Swedish scheme for medicines which are fully or partly paid by public funds.

Orphan medicinal products – the term used in this report to refer to medicinal products used to treat rare diseases.

Threshold – maximum acceptable ICER.

Outcome-based payment model – when payment for a medicine is conditional on an outcome realised after treatment has been provided. This can involve different types of outcomes, such as the magnitude of health gains in terms of quality of life or survival.

1 Background and approach

1.1 Government commission to TLV based on conclusions from previous work

1.1.1 TLV has received a renewed government mandate in precision medicine and ATMPs

The Government has mandated the Dental and Pharmaceutical Benefits Agency (TLV) to continue the work to develop methods for health economic evaluations of precision medicine and payment models for advanced therapy medicinal products (ATMPs) that the Agency began in the previous government mandate, *How should we assess and pay? Health-economic assessments and payment models for precision medicine and ATMPs* (S2020/04362).

In the renewed mandate, TLV will build on the proposals made by the Agency in its previous report. TLV will also use simulations to evaluate how models and tools, such as outcome-based payment models, address the risks and uncertainties associated with many new medicines, in particular ATMPs. The models and tools will be used to ensure that the cost of treatment with ATMPs is reasonable.

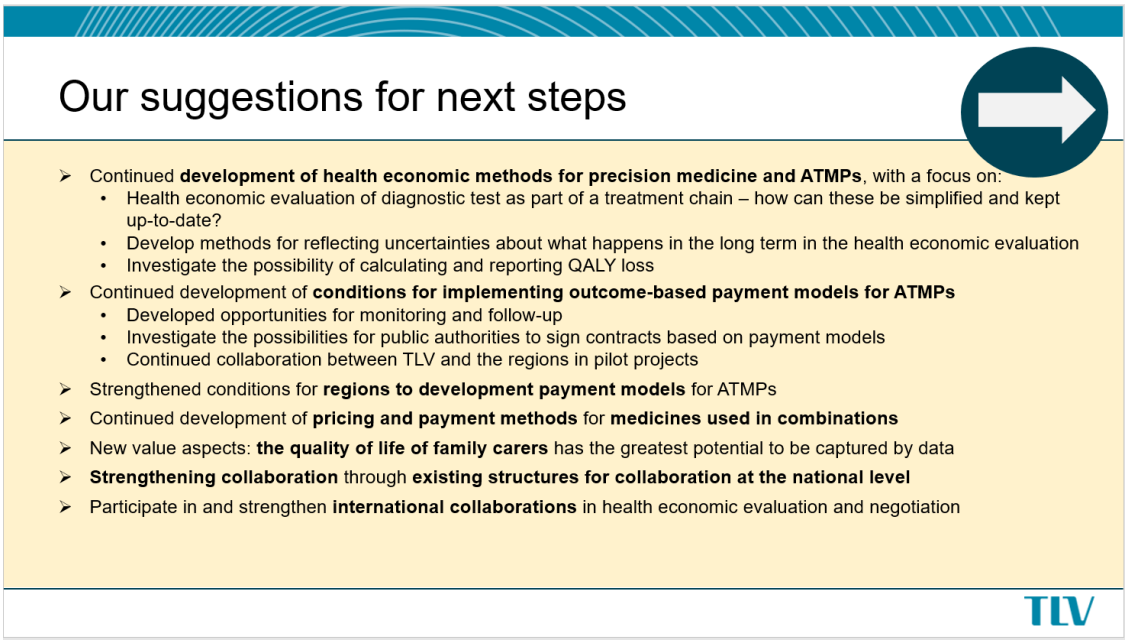
The previous government mandate ran from February 2020 to April 2021 and was reported to the Government Offices on 30 April 2021.

1.1.2 In the previous work, TLV drew a number of conclusions and made suggestions on what further work should focus on

The development of precision medicine and ATMPs is a very positive development. It holds out the hope of major health gains for patients suffering from serious diseases and offers new opportunities for early diagnosis and more accurate treatment choices. One challenge, however, is that companies often demand a very high price for treatments. Health economic evaluations are needed to determine whether the benefits of treatment, in terms of health gains, are commensurate with the costs.
However, conducting these is complicated by the fact that we often have limited data and thus insufficient knowledge about what the health gains of these treatments actually are, particularly in the long term.

In its report on the previous mandate (1), TLV described the challenges that it considers most central to health economic evaluations of precision medicine and ATMPs, and also made suggestions on how to address some of these challenges. We also set out our view of the potential for the use of new types of payment models for ATMPs.

Below is a summary of the suggestions for next steps provided in the report of the previous mandate.



1.1.3 Many of the questions are not unique to ATMPs or precision medicine, but ATMP evaluations present specific challenges

TLV makes decisions on price and subsidy under the Pharmaceutical Benefits Act (2002:160) [lag om läkemedelsförmåner m.m.], inter alia for certain medicines within precision medicine. These decisions are made by the Pharmaceutical Benefits Board. ATMPs are medicines used in inpatient care, referred to as in-patient medicines. TLV is also responsible for carrying out health economic assessments of selected in-patient medicines. In these cases, TLV presents its assessment in a document intended for the New Therapies (NT) Council, which then issues recommendations on the use of the medicine. TLV's health economic evaluations are part of the NT Council's decision-making process. However, the methods used by TLV in health economic evaluations are the same whether the evaluation is of a in-patient medicineor a reimbursed medicine, and the appropriateness of the method depends on the characteristics of the medicines.

TLV's assessments are based on the ethics platform and its three principles: *The human dignity principle*– healthcare must respect the equal value of all people; *The needs-solidarity principle* – those with the greatest medical needs should have access to more healthcare resources than other patient groups; and *The cost-effectiveness principle* – the costs of using a medicine must be reasonable from a medical, humanitarian and socioeconomic standpoint.

Health economic evaluation for precision medicine products is inherently no different from the evaluation of many other types of medicines where evaluations are conducted on a limited body of evidence. However, ATMPs present a number of specific challenges. They are often one-off treatments, and if the full cost is paid at the time of treatment, there is no way to stop payment if the effect should cease. In addition, the medicines are often highly priced by the companies, based on an expectation of a long-lasting and significant effect. The risk for payers is therefore that they pay the cost of a long-lasting effect at the time of treatment, for which there is uncertainty as to whether or not it will be realised. This,

combined with uncertainties about other factors in the health economic assessment, means that payer risk is often significant.

1.2 Main questions of the work

In the mandate presented in this report, TLV has chosen to focus on some of the questions that we considered important to investigate further in our April 2021 report. TLV also reflects on some questions that were not discussed in the previous report, but which relate to factors that may influence TLV's decision-making.

In this report, some questions are based on characteristics that are particularly relevant to ATMPs, while other questions are based on a more general evaluation perspective.

Below we detail the questions we have investigated, which are divided into four main parts in the report; see Figure 1. Not all parts are directly related to each other, but are based on questions that TLV has identified as important to investigate and raise for further discussion or implementation.

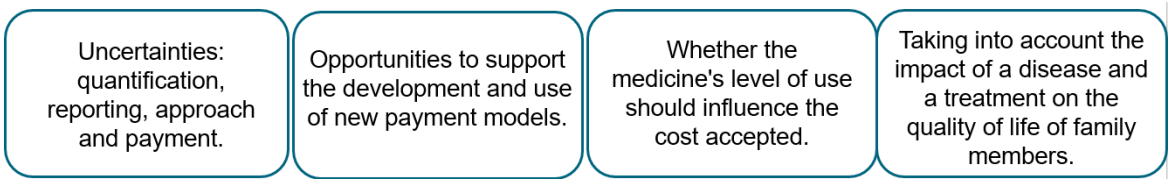


Figure 1: The report is divided into four main parts

Part 1: How uncertainties in health economic evaluations can be quantified, reported and managed

In this report, TLV explores four questions related to how uncertainties in health economic evaluations can be reported, managed and taken into account in calculations, and how they may affect decision-makers. The results of the analyses are presented in Chapter 2. The questions are:

- How can TLV more clearly report the uncertainties in the health economic evaluations?
- Is it reasonable to differentiate the amount of uncertainty accepted based on the magnitude of the health gain lost by delaying treatment?
- For ATMPs, how can we calculate an ICER for the base case that reflects that there is a probability of different outcomes of duration?
- How can the risk-reducing effect of outcome-based payment models for ATMPs be analysed and demonstrated?

Part 2: How can TLV support the development and use of payment models developed for ATMPs?

TLV believes that outcome-based payment models have the potential to address many of the challenges associated with ATMPs. In this work, reported in Chapter 3, we explore how TLV can and should support the evaluation and use of outcome-based payment models for in-patient medicines such as ATMPs, based on the Agency's current mandate and regulatory framework.

Part 3: Should the total usage of a medicine play a larger role in pricing?

In Chapter 4 of the report, we describe why TLV believes there is a case for a more comprehensive analysis of whether a medicine's level of use – in terms of volume or total cost – should play a greater role in TLV's decisions.

Part 4: Should the impact of a disease and treatment on the quality of life of family members be included in health economic calculations and decisions?

The aim of this report is to investigate whether the impact of a disease or treatment on the quality of life of family members should be taken into account in decision-making and, if so, how this can be done. The results are presented in Chapter 5.

1.2.1 Some of the proposals from the previous work are not addressed in this report

In the previous work, TLV described the challenges of pricing medicines used in combinations, and then proposed development work with industry and the regions to find solutions. The regions (via the NT Council and the Swedish Association of Local Authorities and Regions (SKR)) and industry (via Läkemedelsindustriföreningen (LiF)) have initiated development work with the aim of achieving practical solutions in the short term that will improve the conditions for combination therapies to be assessed as cost-effective. TLV is not a partner in the project, but provides support by contributing expertise and knowledge through participation in working groups and as reference persons.

In the previous work, TLV also identified a need for further investigation of how simpler, yet informative, health economic evaluations of non-pharmaceutical types of products in precision medicine, including diagnostic tests, can be made. This investigation could not be prioritised within this mandate.

1.3 Methods for answering the questions of the work

The work is largely based on the extensive investigative work carried out in the previous mandate. As the work has been based on questions that TLV's administrators are often confronted with, we have made extensive use of the Agency's expertise in health economics, medicine, law and data monitoring.

In addition, two external research groups have been consulted in the project. In order to analyse and answer questions regarding the possibilities of including caregivers' quality of life in health economic calculations, TLV has collaborated with a research group at the Department of Learning, Informatics, Management and Ethics (LIME), Karolinska Institutet, consisting of Emelie Heintz, Kinza Degerlund Maldi, Arpana Sharma, Bobby Simarmata and Thomas Davidson. Their work and findings are presented in a separate supporting report (2). In the study on quality of life for family members, TLV has also been in contact with NICE in England and Norwegian Medicines Agency in Norway to learn about their experiences in considering impact on family members in health economic evaluations. In March 2022, TLV hosted two webinars on

this topic. TLV has also been in dialogue with the NT Council and researchers from the National Centre for Priorities in Health at Linköping University.

To analyse questions related to uncertainties in health economic evaluations, TLV has collaborated with a research group consisting of Martin Henriksson and Lina Gruneau at the Centre for Medical Technology Assessment, Linköping University, and Mikael Svensson at the School of Public Health and Community Medicine, University of Gothenburg[1]. Their work is presented in a separate report that is based in part on the supporting report that was produced in connection with the previous government mandate (3) (4).

The supporting reports are independent of this report, and the respective authors are responsible for the content and results.

Jonas Björnerstedt at Södertörn University has contributed to the development of a tool to simulate the effects of payment models.

[1] Martin Henriksson is a full member of the Pharmaceutical Benefits Board and Mikael Svensson is a substitute member.

2 Uncertainties: quantification, reporting, attitude to and payment

2.1 Uncertainties in health economic evaluation of new medicines

Describing uncertainties is a key part of health economic evaluations. At the time of the evaluation, TLV often has limited knowledge of many of the factors that influence the outcome of the health economic evaluation and assumptions therefore need to be made. Some of the factors that often contribute to uncertainty are estimates of health-related quality of life, consumption of healthcare resources and treatment effects over time.

In this chapter, we address a number of questions about how uncertainties in a health economic evaluation can be quantified, reported and managed. In a first section, we present a number of examples of how TLV can describe uncertainties in health economic evaluations in a more consistent way. This applies to all types of medicines and investigations. In the subsequent section, we discuss the principal question of whether it is reasonable to differentiate the level of uncertainty that is accepted based on the long-term impact that delaying treatment would have on the patient's health. In the third section, we present a method for calculating ICERs for ATMPs with a potentially long-lasting effect, to reflect that there is a probability of differences: *a probability-weighted ICER*. We focus here on the duration of the effect because this is a key uncertainty for ATMPs – however, it should not be interpreted as being the only uncertainty. In the final section, we describe how a probability-weighted ICER can be used to show the risk reduction that an outcome-based payment model provides to the payer in terms of reduced ICER.

The chapter uses the terms *ICER* and *cost per QALY gained* interchangeably to refer to the measure used by TLV to describe the cost per unit of health gain. However, the meaning is the same.

2.2 Reporting uncertainties more clearly in the health economic evaluation

2.2.1 TLV sees several reasons for reporting uncertainties in a clearer and more consistent way than is currently done

TLV reports uncertainty in its health economic evaluations through a number of sensitivity and scenario analyses. These analyses adjust one parameter at a time or several at the same time in order to identify those that have the greatest impact on the outcome of the health economic analysis. These analyses are usually based on the assumptions

made by TLV in the base case. Which sensitivity analyses we consider most appropriate depend on the individual case and practice. In the evaluations, TLV also discusses uncertainty in individual parameters and in the overall results.

TLV sees several reasons for presenting uncertainties in health economic evaluations in a more uniform way than is currently done: a clear and recurrent structure is likely to make it easier for decision-makers and recipients of the evaluation to assimilate information that is recurrent in many cases. Although the way uncertainties are reported does not in itself reduce uncertainty, it increases the transparency of the investigation that has been carried out and the understanding of the parameters and assumptions underlying the proposal for a decision. One of the conclusions of the previous mandate is that it is important to distinguish between uncertainties in estimated ICERs and uncertainties about whether ICERs are above or below the level considered reasonable by the decision-maker. This is something that applies to all treatments that TLV evaluates, not just ATMPs and precision medicine.

2.2.2 There are different methods for clarifying the uncertainties in the health economic analysis

TLV has begun internal work to review how we can more clearly quantify and report on the uncertainties in a health economic evaluation. This work includes both reviewing how uncertainties can be reported in a more systematic way than at present, for example through recurrent tables, and reviewing whether it is reasonable to carry out additional sensitivity analyses in certain cases.

As part of this mandate, TLV commissioned a supporting report from a group of health economics researchers on how uncertainties in health economic evaluations can be calculated (3). The report advocates, among other things, the use of *probabilistic sensitivity analysis* (PSA). In a deterministic calculation, which TLV currently uses, a point estimate is used for each parameter. In a PSA, a statistical distribution, with mean and standard error, is assumed for the parameters. Repeated simulations in which different parameter values are “drawn” from the distribution produce a result showing the proportion of simulations below and above the threshold (maximum acceptable ICER). An advantage of a PSA is that it can capture the uncertainty in all parameters simultaneously (3). A prerequisite for TLV to perform a PSA is that the company has included one in its health economic model.

2.2.3 There is a need to more clearly illustrate what the health economic model predicts

A health economic model assumes a number of health stages – specific to the condition in question – between which patients move. However, it can be difficult to determine the plausibility of the so-called transition probabilities that have been assumed – the probability that the patient will move from one health stage to another – based on a set of numbers alone. TLV therefore believes that there are advantages to presenting the model's predictions graphically. Figure 2 below shows an example of such a graphical illustration from Gruneau et al (3). The figure shows the proportion of patients

who, according to the model, are in a particular health state at a particular time. How and when it may be relevant to illustrate results in this way depends on the individual case and also on the type of health economic model submitted by the company.

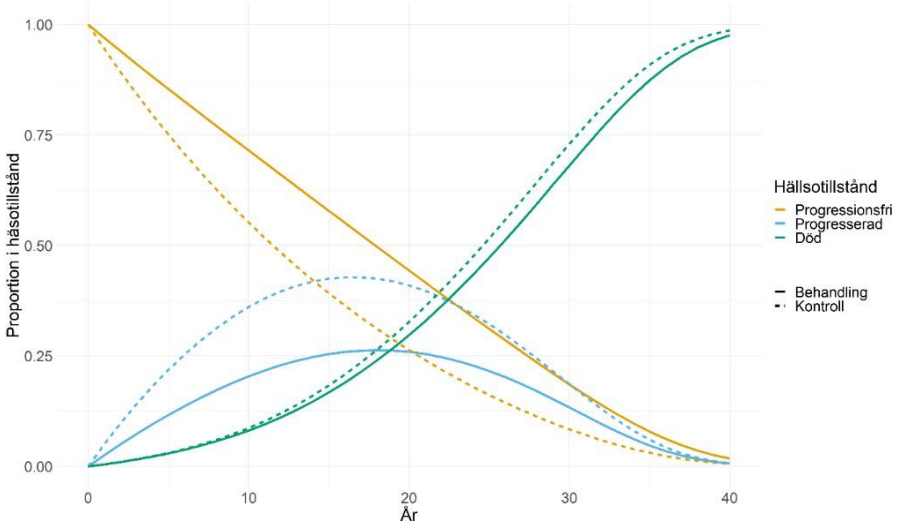


Figure 2: Results from a health economic model looking at the proportion of patients in different health states at given points in time (3)

TLV intends to continue its internal work on how to identify and report on uncertainties in health economic evaluations, based in part on the conclusions in the supporting report.

2.3 Taking the consequences of waiting to introduce a new medicine into account

Later in this chapter, we discuss ways to reduce decision uncertainty and the risk that the cost exceeds the actual health gain in clinical practice. However, some uncertainty will always remain. This means that the decision-maker's approach to uncertainty may play a role in whether the medicine is made available to patients.

Waiting to use the medicine until better evidence is available may be a strategy for the decision-maker to reduce the risk that the cost exceeds the actual health gain. This is because knowledge about the benefits of the medicine increases over time. One factor that may need to be taken into account is the magnitude of the health gain lost by delaying treatment. This is not captured in the estimated ICER and only to some extent in the severity assessment. In other words, even if the severity, estimated ICER and uncertainties are the same in evaluations of two different medicines, there may be reasons to make different decisions. This is because the consequences for patients of waiting for better evidence before starting to use the medicine may be different. In the previous report, we concluded that the question of whether it is reasonable to differentiate the level of uncertainty that is accepted should be further investigated.

2.3.1 TLV's conclusion is that it is reasonable to accept different degrees of uncertainty in different situations

In the current work, TLV has concluded that it is reasonable to differentiate the level of uncertainty that is accepted, depending on the long-term impact on the health of the average patient.

TLV argues that this idea is consistent both with how individuals actually act and with formal decision theory. Most patients would be more likely to use a medicine with an uncertain efficacy and safety profile – more likely to take a risk – if the disease with current treatment leads to rapidly deteriorating health. It is also consistent with more formal decision theory, i.e. theories about how decisions should be made. Value-of-information is the established theoretical framework that describes how to think about the value and consequences of waiting to introduce new treatments in order to obtain better evidence (3). One factor that plays a role in these analyses is the magnitude of the health gain loss that delaying treatment causes for patients. Appendix B of this report elaborates on this reasoning with a simple numerical example.

The European Medicines Agency (EMA), which makes decisions on marketing authorisation for medicines, can also be said to act on this principle when it can grant *conditional authorisation* when one of four criteria is based on “the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required” (5).

Already today, however, TLV often approves applications for subsidies for new medicines where there are considerable uncertainties, particularly as regards medical efficacy. The reasoning here should therefore not be interpreted as TLV becoming more willing to accept even greater uncertainty, but as a differentiation: how much uncertainty is accepted when the magnitude of health gain lost by delaying treatment is large compared to how much uncertainty is accepted in situations where this is not the case.

Nor should the reasoning be interpreted as raising accepted levels for ICER. In the case of a medicine where the magnitude of health gain lost by delay is large, but where we know with certainty that the ICER is above the accepted level, the reasoning here is not applicable – there is no decision uncertainty.

2.3.2 Practical implementation requires some consideration

There are some questions to consider before any practical implementation.

Risk of double counting

In the investigation, we have encountered the question of whether there is a risk of double counting by considering the health gain or severity twice in the decision-making process.

It is important to apply this in such a way that the same factor is not taken into account more than once; that no double counting occurs. The magnitude of the health gain lost from delaying treatment will depend on the quality of the medicine. In other words, the greater the health gain from treatment, the more the patient loses by not receiving treatment.

There is also a risk that the severity of the condition is considered twice, as the size of the health gain lost by delaying treatment will also depend on the severity of the condition. This risk is real, and can be greater or lesser depending on how severity is assessed. TLV's current assessment of severity has four categories, but a large proportion are considered to be in the highest category of very high severity. Taking into account the health gain lost by delaying treatment will therefore be a major way of distinguishing between conditions that are assessed as very severe. Even if a condition is very severe, immediate treatment is not always as important.

Is potential lost health gain measured in terms of QALYs a useful measure to capture the consequence of waiting for treatment?

Ideally, a quantitative measure would be preferable to capture the lost health gain, for example in terms of the number of QALYs. However, TLV believes that a calculation of such a measure will often not be possible based on the health economic models we receive from companies. However, a rough categorisation can be made that is still sufficient; such as *small*, *medium* or *large* loss in health gain from delaying treatment.

Perhaps the biggest challenge in practical application is to determine what the balance should be between uncertainty and the health gain lost by delaying treatment. How this is applied in practice needs to be developed as part of TLV's ongoing management.

2.4 How uncertainty about the duration of effect for ATMP can be reflected in calculated ICER

In the previous report, TLV discussed a proposal to calculate ICERs in TLV's base case in a somewhat different way than at present for those ATMPs that potentially have very long-lasting effects. The aim of such a method is to ensure that the base case better reflects the fact that there are probabilities of different outcomes – in particular in terms of duration of effect. We refer to this method as probability-weighted ICER and it can be said to be a type of probabilistic analysis (3).

Below, we discuss this method in more detail by comparing it with the methods commonly used today in cases where there is uncertainty about how long the effect benefit of a new medicine will persist.

The reason why the probability-weighted ICER approach may be particularly relevant for one-off treatments such as ATMP is that payment for the full lifetime benefit is made at the time of treatment. The duration of the effect is therefore even more crucial for the actual ICER realised for ATMPs than for continuous treatments, as they can be discontinued – as can payment – if the desired effect is not achieved. If the probability weighting method proves to be informative, it may in the future also

be applied to other medicines and also include other types of outcomes than duration of effect. To clarify our reasoning in this chapter, we use simplified hypothetical examples.

Example A

We consider a disease that rapidly progresses with currently available treatment. The patient's health-related quality of life declines over time, and after 10 years the patient has died. A gene therapy administered as a one-off treatment is approved for use.

It is hoped that the gene therapy will prevent the disease from progressing and that the patient will have a lasting high quality of life. The clinical trials that have been conducted do not include a control group and have a short follow-up period. This means that at the time of approval there is only limited knowledge about the medicine: How long will the effect last? How good is the effect for the duration?

Figure 3 shows an ideal outcome where the effect of the medicine results in the patient having a good quality of life immediately from the start of treatment and where the effect will persist for 40 years.

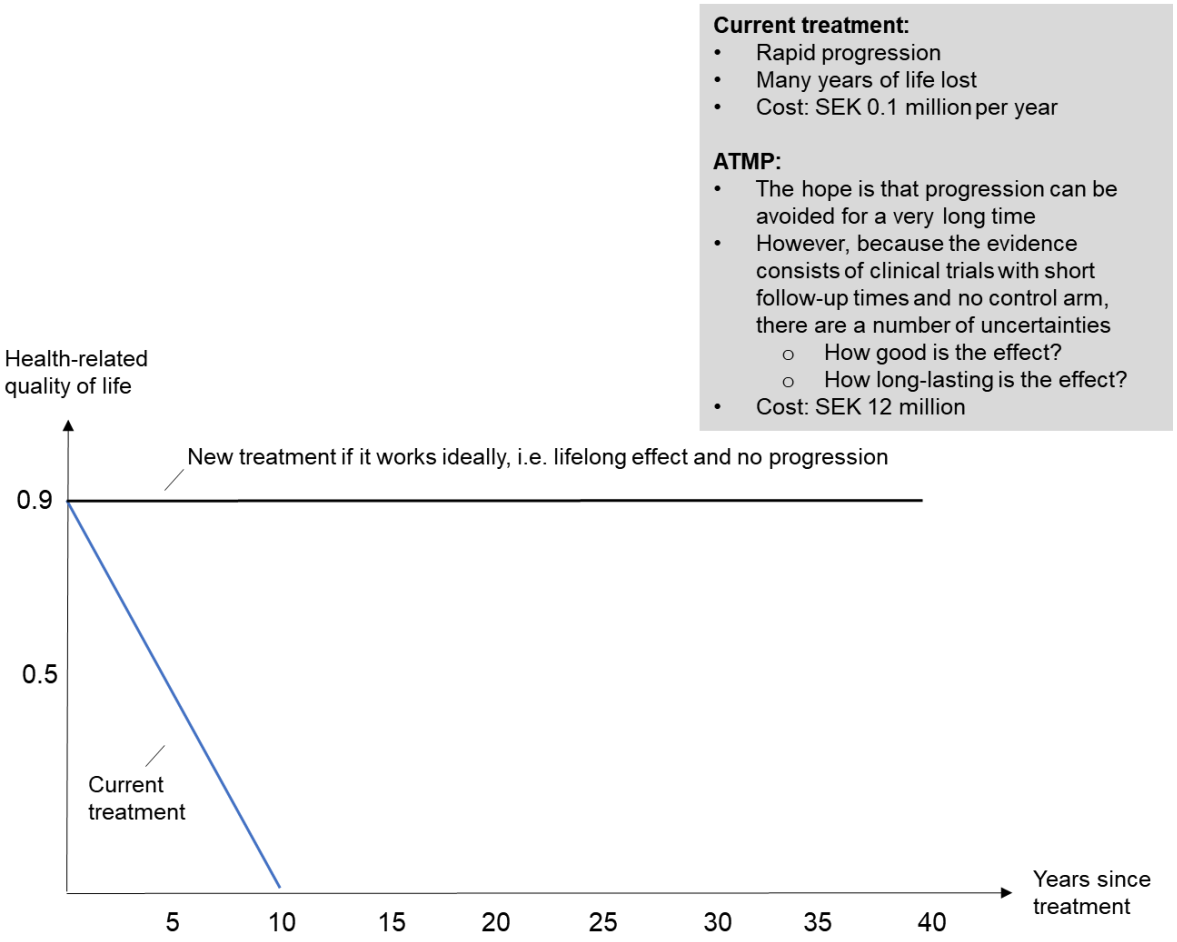


Figure 3: Health development with current treatment and with gene therapy in the ideal case

However, instead of the ideal outcome in Figure 3, the situation may be as indicated with dotted lines in Figure 4. In this case, the patient has an initially good, but diminishing, effect for the first 15 years, after which the effect of the treatment vanishes and the disease progresses rapidly.

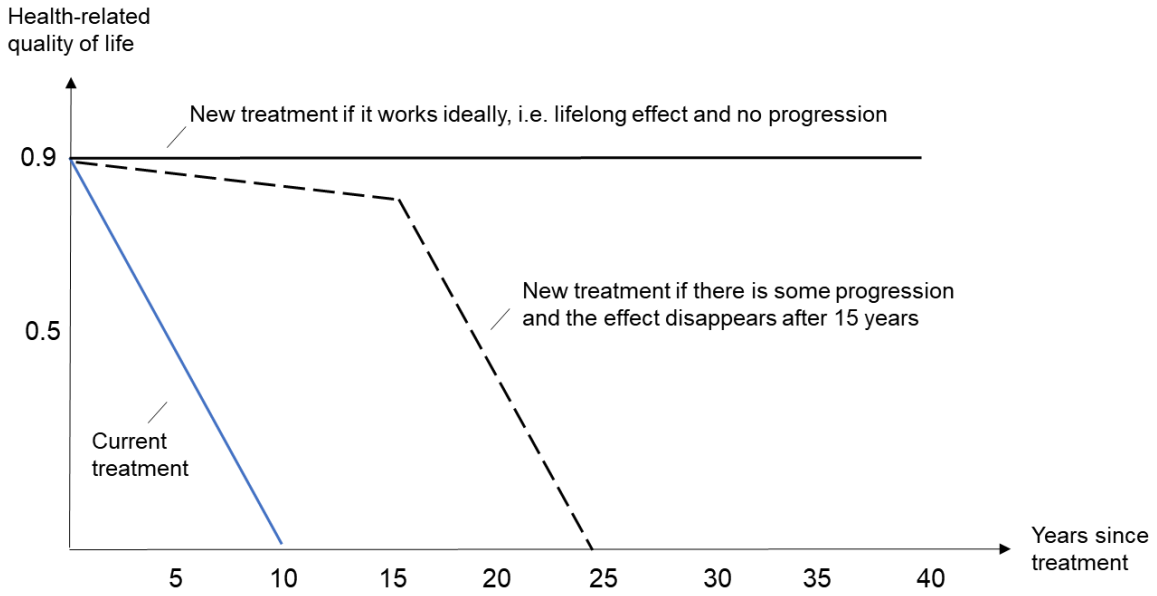


Figure 4: Health development with current treatment and with gene therapy if the effect vanishes after 15 years

2.4.1 There are different ways of reflecting uncertainties in the duration of the effect when calculating ICER

The question that TLV discusses in this section is how the calculation of ICER can be made to reflect that there is a probability that the outcome will not be as in the ideal situation in Figure 3, but instead as in Figure 4 – or in a completely different way.

If TLV has assumed in the base case that the disease will not worsen if the patient is treated with the gene therapy, and that this is a lifelong effect, then we have indirectly assumed that the probability of a worse outcome than the ideal is zero percent – which is very rarely true. Therefore, even in situations where the most likely outcome is a lifelong effect, an assumption of
lifelong effect is rarely reasonable. The ICER in the base case should therefore somehow reflect that the ideal outcome is not necessarily realised. Today, the *shortened time horizon* method or the method of *assuming that the effect lasts a certain number of years* is often used to handle with this.

Shortened time horizon

With the shortened time horizon approach, health gains and costs are only calculated for a limited number of years into the future. It is a method that may be reasonable when a treatment is not expected to result in any health gains or cost differences after a certain point in time – after which both health and costs are the same regardless of what treatment the patient received in the past. The typical case is a pain-relieving treatment where the effect disappears when the treatment ends and there is no remaining benefit or cost difference between the treatment arms.

The method is less suitable if the treatment affects survival. If a higher proportion of patients receiving the new medicine are alive at the time

the time horizon ends, then the additional survival after this time will not be included in the estimated health gain (QALY gain).

Sometimes, the method is used even though there may be residual long-term health gains from a treatment. This may be because the health economic model does not allow for other ways of adjusting for uncertainties about the long-term health gains. It becomes a cruder approach, but sometimes the only one possible.
It may also be because TLV believes that there is no evidence for the long-term health gains modelled by the company – that it becomes too speculative to assume this.

TLV's assessment is that this is a less suitable method for dealing with uncertainty about the duration of ATMPs with potentially very long-lasting effects, as it risks underestimating health gains and cost benefits. For a continuously administered medicine, shortening the time horizon of the model excludes both health gains and cost *increases* compared to the treatment option after this time. These effects cancel each other out to some extent. However, doing the same for a one-off treatment such as ATMPs often excludes health gains and cost *savings*. This is because when the full cost of ATMP is paid directly but there is a continuous annual cost for the comparator, then the difference in total treatment cost decreases with each passing year – i.e. there is no annual incremental cost for ATMP. Thus, if we use a shorter time horizon for ATMP we exclude both potential health gains after this point and the annual savings of not having to pay for the comparator.

However, the shortened time horizon method may still be reasonable to use in sensitivity analyses to see how the model behaves.

Effect lasts for a certain number of years

Another method for handling uncertainty about the duration of the effect is to assume that the effect benefit disappears a certain number of years after the treatment has been provided, but that the time horizon in the analysis is still lifelong.

The difference in results between this method and the shortened time horizon method can be explained by taking an example with a treatment that has a lifelong effect. If we use the approach that the *effect lasts for a certain number of years* and set this to 5 years, then a higher proportion of patients who received the new medicine after 5 years will be alive than those who received the established treatment. After 5 years, the patients are assumed to have the same risk of dying regardless of treatment. However, the fact that more people who received the new treatment after alive after 5 years means that the health economic model predicts health gains (QALY gains) from the new medicine even after year 5.

For example, say that 80 out of 100 patients who received the new medicine live after 5 years, while the same figure for patients who received the established treatment is 20 out of 100. If we use the *shortened time horizon* method and set it to 5 years, we assume, in practice, that all patients die at this point. If, on the other hand, we use the *effect lasts for a certain number of years* method, we include all the life years gains for the extra 60 people still alive after 5 years.

There are also disadvantages to the *effect lasts a certain number of years* method, one of which is that the calculation does not reflect the fact that there is a probability that the effect will last a longer or shorter amount of time. It is certainly not the case that an assumption of, for example, 15 years of lasting effect should be interpreted to mean that TLV considers that the effect benefit disappears after exactly 15 years. Rather, it is an assumption that reflects a trade-off in which the actual duration of the effect may be either longer or shorter. However, the method may still be misleading. Since the calculated ICER is not linear with respect to duration, the ICER for 15 years' duration will not be the same as the average of the ICER for 5 years' duration and the ICER for 25 years' duration.

Later in this section, we also show that if an outcome-based payment model is applied, which means that the payment is different if the effect lasts for 5 or 25 years, then the problem of setting the duration to, say, 15 years becomes even greater. This is because the calculated ICER will then be even more non-linear in duration. We will return to this in Section 2.5.

Table 1 lists some of the ATMPs that TLV has evaluated to date, with a summary of the main uncertainties and how these have been addressed.

Table 1: Examples of how TLV has managed uncertainties in a number of ATMP evaluations within the in-patient medicines mandate

Product name (year evaluated by TLV)	**Medicine for**	**Main uncertainties in evaluation**	**How TLV managed uncertainties in the ICER calculation**
Alofisel (2018)	Complex anal fistulas	Duration of effect	Results presented as a range based on different time horizons in the model (shortened time horizon)
Zolgensma (2022)	Spinal muscular atrophy (SMA)	- Duration of effect - Effect relative to comparator	- No base case - Scenario analyses in which duration of treatment effect were varied. - No analysis for subgroups lacking data on relative effect
Yescarta (2018)	Large B-cell lymphoma	Proportion of patients potentially cured and their mortality risk	- No base case. - Scenario analyses in which assumptions about the proportion of patients cured were varied
Kymria (2019)	B-cell acute lymphoblastic leukaemia (ALL)	Proportion of patients cured	- No base case. - Scenario analyses in which assumptions about the proportion of patients cured were varied
Luxturna (2019)	Vision loss due to inherited retinal dystrophy	Treatment effect over time, magnitude of health-related quality of life gain	The results are presented as a range that depends on different assumptions: duration of effect, disease progression beyond the time when the effect is assumed to persist (constant), and quality of life weights
Zynteglo (2020, FINOSE)	β thalassaemia	Duration of effect (transfusion independence obtained) and magnitude of survival gain	Two scenario analyses with and without survival gains
Libmeldy (2022, FINOSE)	Metachromatic leukodystrophy (MLD)	Duration of effect	- Two scenario analyses in which the clinical effect was varied

Source: www.tlv.se

Probability-weighted ICER

A third alternative is to assume that there is a certain annual probability that the effect will disappear and to let the ICER in the base case correspond to a weighting of different outcomes. Then the ICER will reflect that there is a probability of different outcomes. As already discussed, TLV believes that this method should be tested for certain ATMPs with potentially very long-lasting effects. Appendix A at the end of the report shows the formula for how we believe the calculation can be done.

The disadvantage of this method is that an assumption has to be made about what the annual probability of the effect disappearing is, and whether it increases or decreases over time. We understand the challenges of estimating these probabilities, but compared to the method of assuming that the *effect lasts a certain number of years*, probability-weighted ICER can:

- Better link clinical evidence to the assumption on the annual probability that effect disappears, as these probabilities should be observable in trials.
- Allow the probability to vary between years – for example, high at the beginning and lower after a certain time.

In addition, even with the *effect lasts a certain number of years* method, an implicit assumption is made about what the annual probability of the effect persisting is, but it is less clear exactly what that assumption is.

It must be possible to vary the probabilities of duration of effect depending on the quality of the evidence on duration of effect for the medicine in question, and depending on the technology on which the specific ATMP is based. Exactly how this can be handled and performed requires further investigation and development work. As experience with ATMPs grows, there will be increasingly better data on these probabilities and how they vary between different types of ATMP technologies.

The different methods result in different ICERs

To show that the different methods of dealing with uncertainty about duration of effect can produce different results on calculated ICERs, we return to the previous example, Example A. Figure 5 shows what the actual realised ICER is depending on the duration of effect. For example, we see that the effect must persist for at least 20 years for the ICER to be less than SEK 1 million, which in the example is assumed to be the maximum acceptable level. We also see that the ICER is strongly non-linear in the duration; it declines much faster at the beginning than at the end.

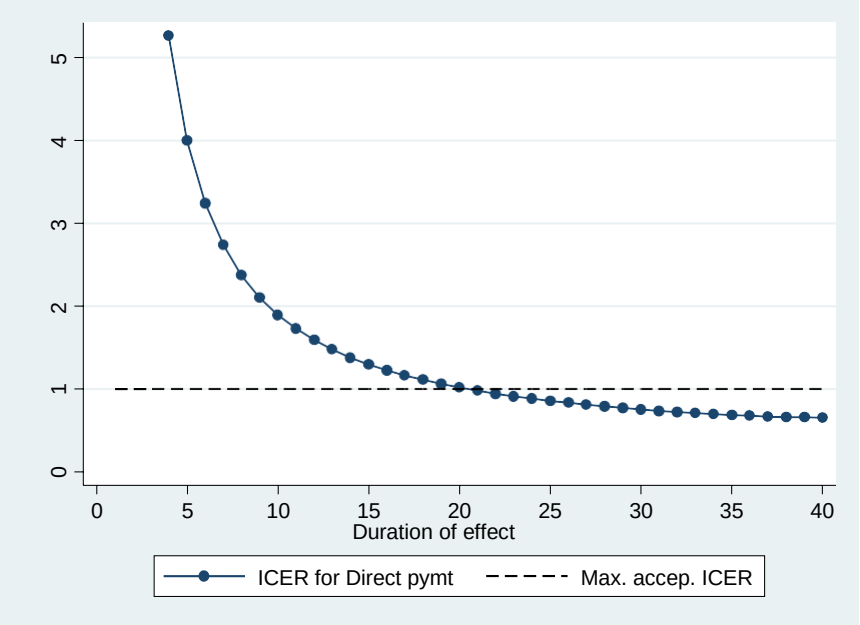


Figure 5: ICER (cost per QALY gained) as a function of different durations of effect

Table 2 shows which ICER we obtain with the three different methods given certain assumptions. We show what the ICER is with the *shortened time horizon* method if it is set to 15 years, and what the ICER is with the *effect lasts for a certain number of years* method if it is assumed that there is no remaining effect after 15 years. With probability weighting, an annual probability must instead be assumed. An annual probability of 4.5 per cent means that after 15 years the cumulative probability that the effect has disappeared is about 50 per cent.

Table 2: ICER using three different methods

Method for handling uncertainty	ICER, with direct payment (SEK millions)
1. Shortened time horizon, assumption: 15 years	2
2. Effect lasts for a certain number of years, assumption: 15 years	1,3
3. Probability weighting, assumption of annual risk of loss of effect: 4.5%	1,2

In this example we get a certain ranking for ICER. However, it is not possible to say in general which method gives the highest or lowest ICER – it depends on the assumptions made with the different methods. The point of the above example is to demonstrate that the choice of method for handling duration of effect matters and can generate different results.

In conclusion, TLV believes that the probability weighting method has theoretical advantages and should be tested. In the next section, we argue that these

advantages become even clearer when outcome-based payment models are used. However, the probability weighting method needs to be tested in actual cases to see how useful it is in practice. A potential risk is that the method may lead to additional work for companies and be time-consuming to investigate for TLV investigators.

2.5 How outcome-based payment models can reduce the risk to the payer of ATMPs

Suppose a new gene therapy for a severe disease is available. It is priced by the pharmaceutical company based on the expectation of a very good and long-lasting effect. But there is no evidence of long-term efficacy because the clinical trial on which the marketing authorisation is based lasted only one year. If the effect is good and long-lasting, the high one-off cost paid at the time of treatment is reasonable. If, on the other hand, the effect in clinical practice disappears after only a few years, the health gain is far from sufficient to justify the cost. In this section, we discuss how outcome-based payment models can be used to reduce payer risk in a situation like this.

2.5.1 ATMPs pose particular challenges – outcome-based payment models have the potential to address some of these

In this report, we use the term outcome-based payment to refer to when the payment to the company is conditional on an outcome that is realised after the treatment has been provided. This can involve different types of outcomes. The magnitude of the health gain, in terms of quality of life or survival, is one type of outcome. Another type of outcome is that the patient starts using a different medicine, which may be a sign that the original medicine is not working as well as expected.

The aim of outcome-based payment models is to reduce the risk that the cost is higher than can be justified based on the actual health gain realised in clinical practice. This has an indirect positive effect on availability: the lower risk for the payer allows the medicine to be used. Given the high uncertainty that often exists for new medicines in general and ATMPs in particular, TLV therefore considers it important that outcome-based payment models are tested. Otherwise, there is a risk of society not providing access to important medicines that later prove to have sufficient efficacy to justify the cost.

In this chapter, the benefit of outcome-based payment models is expressed as reducing payer risk. The alternative is to pay the full amount at the time treatment is provided. However, the advantage for the company – and patients – is that utilisation can be greater because the payer is given a manageable risk. Outcome-based models can therefore be mutually beneficial.

In this chapter, we discuss how payer risk reduction can be demonstrated, i.e. how to see how an outcome-based payment model for ATMPs impacts ICERs. In our analyses, we focus mainly on the health outcome, namely the duration of the effect, as we did in the previous section (Section 2.4). By extension, the same method can then be used for other factors.

There are many practical challenges with outcome-based payment models, which this report does not focus on. However, this should not be taken to mean that TLV considers these to be unimportant – on the contrary, the challenges in practical application are significant and may be what ultimately leads to the models not being used. At the same time, we believe that the best way to increase understanding of the challenges and how they can be addressed is to actually test the application of outcome-based payment. In Section 2.5.4 we briefly highlight some of the practical challenges of finding appropriate outcome measures that can be used in an outcome-based payment model and the challenges of being able to monitor them. In Chapter 3, we outline the possibilities for the Agency to support the development and use of payment models.

2.5.2 Simulations can be used to analyse and describe the impact of different payment models

In TLV's previous report, we discussed outcome-based payment models in detail (1). In order to assess the appropriateness of a payment model, TLV has begun development of a web-based simulation tool. In this tool, the user – such as a company or a payer – will be able to characterise different medical conditions (life expectancy, quality of life over time, etc.) via sliders and choose different payment model constructs. The tool should then be able to simulate the impact of the chosen payment model on, among other things, ICER, budget and company revenues.

In an initial simpler and preliminary version, which has been developed within this mandate, the tool will be based on a number of stylised scenarios (highly simplified characterisations of disease impact and change over time). This simpler version can serve as an educational tool to increase understanding of payment models. The tool can then be further developed in a next step to simulate more complex situations that approximate the health economic models that companies submit to TLV for a health economic evaluation.
It is hoped that the tool can be used to analyse the effects of a payment model for actual medicines.

Follow this link to access the initial version of the simulation tool:
https://tlvanalys.shinyapps.io/simulering-betalningsmodeller/

2.5.3 How can outcome-based payment models reduce payer risk?

In this section, we use results from the simulation tool to discuss outcome-based payment models for two stylised examples that are intended to be similar to ATMP situations. The aim is to illustrate how much risk reduction different types of outcome-based approaches can provide in theory, and how calculations of ICERs need to be made and illustrated in order for the risk reduction to be visible to the decision-maker and payer.

In the simulations below, we use the example used in Section 2.4 as well as a new example.

Example A: Condition that deteriorates rapidly with current treatment and results in few remaining years of life

Example A is the one presented earlier in Figure 4. Figure 6 shows what the ICER would be with *direct payment* and with *a certain outcome-based payment model* where the payment is split over 10 years and the annual payment is only made if the patient still has an effect from the ATMP – i.e. if the disease does not progress as rapidly as with standard treatment. Assuming that the effect persists, the payment is SEK 300,000 per year in years 1–9, and the remainder of the SEK 12 million total assumed cost of this ATMP is paid in year 10.

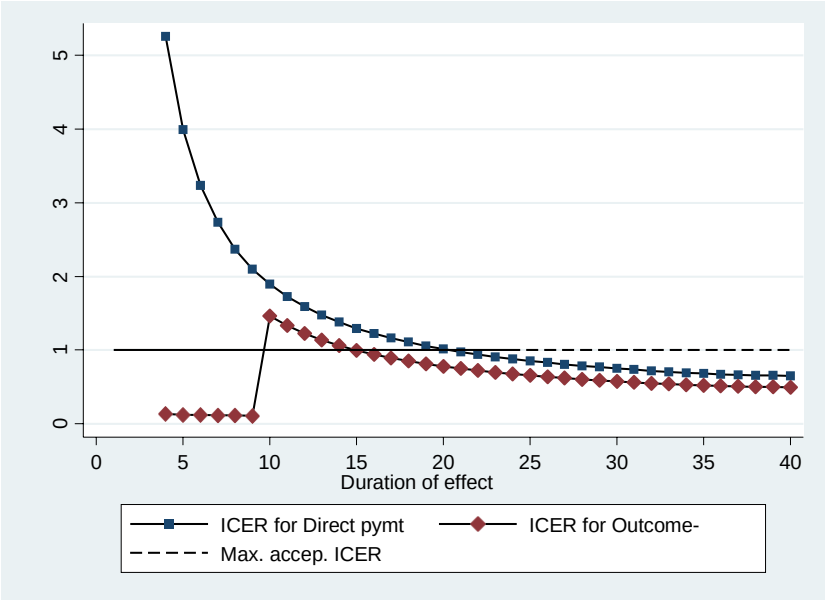


Figure 6: ICER at different durations, with direct payment and with an outcome-based payment model, where SEK 300,000 is paid in years 1–9, and the remainder of the SEK 12 million assumed cost of the ATMP is paid in year 10.

We see in Figure 6 that the outcome-based payment provides good risk mitigation in the first 10 years: even if the effect disappears in years 1–10, the actual realised ICER does not exceed SEK 1 million. After 10 years, the full cost has been paid, and the two curves almost coincide (without discounting, they would coincide completely). With this type of graph, it is thus possible to show how much risk reduction is achieved with the outcome-based payment over different time periods.

However, we also need to calculate a summary measure for the various possible actually realised ICERs – an expected ICER. The graph then shows the advantage of using the probability-weighted ICER method. With a probability-weighted ICER, the entire curve is reflected and the curve is initially below the threshold and then above for a period.[2]

With the *effect lasts for a certain number of years* calculation method, the risk reduction provided by the outcome basis is not visible: the calculated ICER is (almost) the same as if the full payment was made at the time of treatment; see *Table 6*.
The reason is therefore that the *effect lasts for a certain number of years* method only takes into account

[2] However, the probability-weighted ICER is not a simple weighting of the points in the graph.

one point on the red line. The problem is also the same with the *shortened time horizon* approach (see Section 2.4).

Table 3: Estimated base case ICER (SEK millions) with different

Method for handling uncertainty	Direct payment	Outcome-based payment*
1. Shortened time horizon, 15 years	2	2
2. Effect lasts for a certain number of years, 15	1,3	1,3
3. a) Probability weighting, annual risk of loss of effect: 4.5%	1,2	0,7
b) Probability weighting, annual risk of loss of effect: 10% years 1–10, 1% after year 10	1,4	0,5

* Years 1–9: SEK 0.3 million, Year 10: SEK 9.3 million if effect persists; no payment if effect has diminished.

As mentioned earlier, the calculated probability-weighted ICER will depend on the assumed annual probability of disappearance of the effect. The last row of the table shows results for whether the probability is high for the first ten years, and then declines. We now see that there is a larger difference for *direct payment* and *outcome-based payment*, SEK 1.4 million and SEK 0.5 million per QALY, respectively. The reason is that the outcome-based model manages the risk effectively in the first 10 years, precisely when the probability of the effect disappearing is highest.

In summary and firstly, the risk reduction of outcome-based payment is made visible with probability weighting. Secondly, the effect of an outcome-based payment model is that the expected ICER is lower and – in this example – that the ICER is at an acceptable level. If the payer or decision-maker largely wishes to make its decision based on the ICER in the base case, the outcome-based payment model means that the medicine can be put into use and patients can access the treatment, even though the risk is only reduced for the first 10 years. Thus, the outcome-based payment model does not guarantee that the cost does not exceed the benefit – this is unrealistic to aspire to. But the payment model reduces the risk sufficiently for it to be at an acceptable level.

To further illustrate the effect of different payment models and the impact of the annual probability of loss of effect, Table 4 shows what the probability-weighted ICER becomes for four different outcome-based payment models.
These can be illustrated with the same type of graph used in Figure 6 above, which is not done here due to space constraints.

Table 4: Example A: Probability-weighted ICER with different annual risks of loss of effect

	Probability-weighted ICER, SEK millions				
Annual probability of loss of effect, % (in brackets: years when cumulative probability is >50%)	**Direct payment**	**Outcome-based i) Equal payments for 10 years**	**Outcome-based ii) Low payments years 1–9, remainder year 10**	**Outcome-based iii) Equal payments for 5 years**	**Outcome-based iv) Full amount at treatment. Repayment of 80% year 5**
2% (33)	0,88	0,71	0,59	0,75	0,80
3% (23)	1,00	0,77	0,62	0,84	0,87
4% (17)	1,12	0,83	0,65	0,92	0,94
5% (14)	1,24	0,89	0,67	1,01	1,00
6% (11)	1,36	0,94	0,68	1,08	1,06
Years 1–10: 10%, After year 10: 1%	1,40	0,84	0,54	1,04	0,98
Years 1–5: 10%, After year 5: 1%	1,11	0,70	0,54	0,82	0,89

i) The sum of SEK 12 million is divided into equal parts in years 1–10. No payment if effect has diminished.
ii) Sum of SEK 12 million: Years 1–9: SEK 0.3 million; Year 10: SEK 9.3 million. No payment if effect has diminished.
iii) The sum of SEK 12 million is divided into equal parts in years 1–5. No payment if effect has diminished.
iv) The sum of SEK 12 million is paid at the time of treatment. However, if the effect disappears and the condition begins to worsen, 80% of the cost will be reimbursed at the end of the contract period.

The main conclusion that can be drawn from the table is that with *direct payment*, the annual probability of loss of effect plays a major role in whether the medicine is deemed to provide sufficient health gain to justify the cost – i.e. an ICER of less than SEK 1 million. With outcome-based payment models, the annual probability matters less, as the aim is to provide "insurance" against loss of effect. The best risk reduction, in the sense that the ICER does not change much as the annual probability of the effect disappearing increases, is provided by *Outcome-based (ii)* with low payment in years 1–9 and the remainder in year 10.

A number of other payment models are of course possible, as well as a number of different "trajectories" for how the annual probability of the effect disappearing evolves over time. The aim of the simulation tool that TLV has begun to develop is to be able to simulate many different scenarios in order to increase understanding of the factors that influence how a payment model contributes to risk reduction.

Example B: Condition where current continuous treatment is expensive but the condition does not progressively worsen or lead to shortened life

In Example A, the high cost of an ATMP is justified by a very large health gain. In Example B, the cost of the ATMP is SEK 8 million. The health gain is much smaller than in Example A because there is already a fairly effective treatment; see Figure 7 below. However, the current treatment is very expensive, at SEK 1 million per year. So, the price of ATMP is largely justified by the fact that in the long run a saving is made if the effect of the ATMP proves to be long lasting.

However, if the ATMP does not prove to have as good an effect as expected, then the patient is assumed to switch to the previous treatment. Thus, in addition to a missed improvement in quality of life, there is a high cost of paying for the previous continuous treatment.

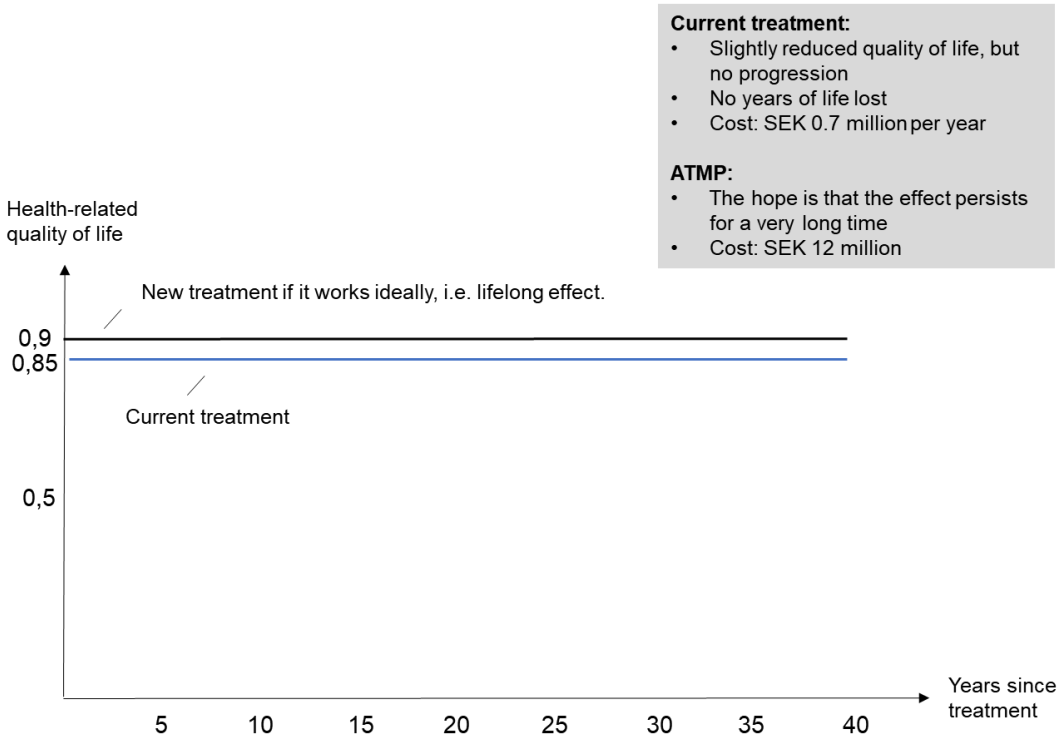


Figure 7: Quality of life over time with current treatment and with ATMP given that the effect last for 40 years.

In Figure 8, we see what the actual realised ICER becomes with different duration of effect. As in Example A, 20 years' duration of effect is required to achieve a reasonable ICER. if we use the *effect lasts for a certain number of years* method and this is set to 20 years, the treatments in Examples A and B would have the same calculated ICER.

We also see that the variation in ICER in Example B is much larger than in Example A. If the effect were to persist for only 10 years, then the actual realised ICER in Example A is SEK 2 million while in it is about SEK 12 million in Example B. In years 10–20, the ICER is still high. Figure 8 also shows the effect of an outcome-based model with a very low payment in the first 9 years: SEK 700,000 per year, and the remainder of the total cost of SEK 12 million is paid in year 10.

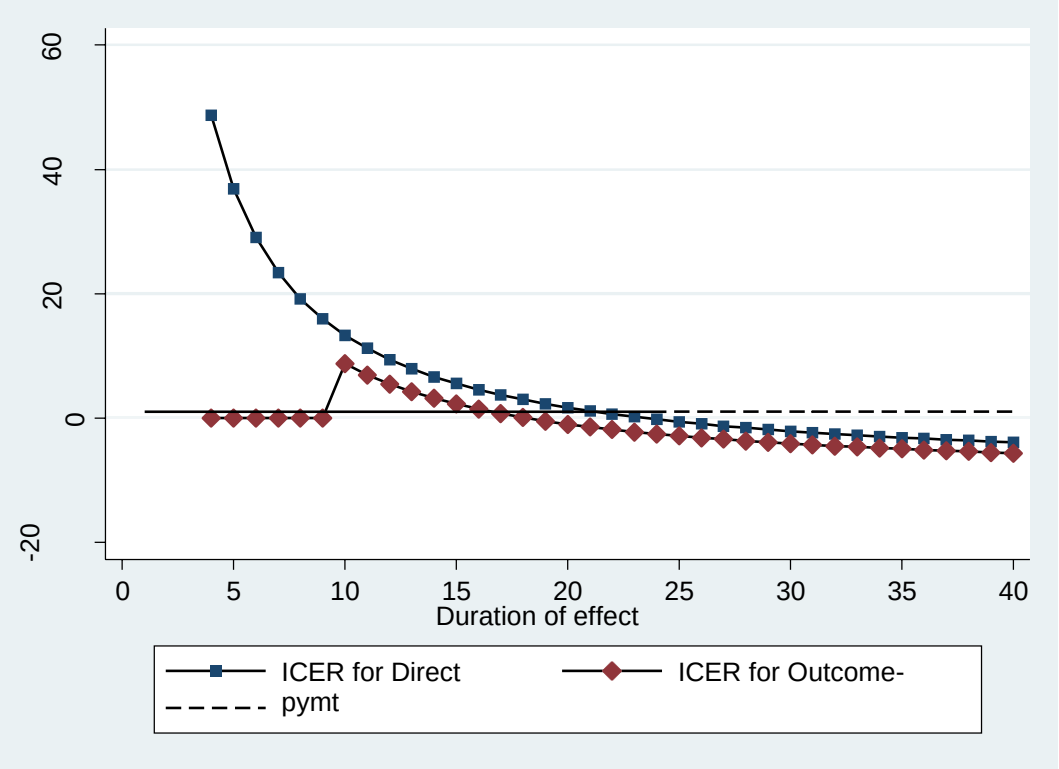


Figure 8: ICER at different durations, with direct payment and with an outcome-based payment model, where SEK 700,000 is paid in years 1–9, and the remainder of the SEK 12 million assumed cost of the ATMP is paid in year 10.

Table 5 below shows the probability-weighted ICER for the same payment models as in Table 4. The conclusion here is that since the ICER varies very widely, the need for risk mitigation through an outcome-based payment model is even greater than in Example A. Of the payment models, the one that works best in Example A is *Outcome-based ii)*. With it, ATMP is dominant (lower cost and health gain) regardless of the probability of the effect disappearing.

Table 5: Example B: Probability-weighted ICER with different annual risks of loss of effect

	Probability-weighted ICER, SEK millions				
Annual probability of loss of effect, % (in brackets: years when cumulative probability is >50%)	**Direct payment**	**Outcome-based i) Equal payments for 10 years**	**Outcome-based ii) Low payments years 1–9, remainder year 10**	**Outcome-based iii) Equal payments for 5 years**	**Outcome-based iv) Full amount at treatment. Repayment of 80% Year 5**
2% (33)	Dominant	Dominant	Dominant	Dominant	Dominant
3% (23)	1,20	Dominant	Dominant	Dominant	Dominant
4% (17)	2,95	Dominant	Dominant	0,06	Dominant
5% (14)	4,65	1,44	Dominant	1,20	0,60
6% (11)	6,26	0,11	Dominant	2,24	1,25
Years 1–10: 10%, After year 10: 1%	6,41	Dominant	Dominant	1,39	Dominant
Years 1–5: 10%, After year 5: 1%	2,48	Dominant	Dominant	Dominant	Dominant

* "Dominant" means that the new treatment leads to better effect at lower cost compared to the comparator.
i) The sum of SEK 12 million is divided into equal parts in years 1–10. No payment if effect has diminished.
ii) Years 1–9: SEK 0.7 million; Year 10: SEK 5.7 million. No payment if effect has diminished.
iii) The sum of SEK 12 million is divided into equal parts in years 1–5. No payment if effect has diminished.
iv) The sum of SEK 12 million is paid at the time of treatment. However, if the effect disappears and the disease begins to progress, 80% of the cost will be reimbursed at the end of the contract period.

In summary, the purpose of discussing the two stylised examples presented here is to show that it is not obvious how good the risk reduction provided by a particular outcome-based payment model is in a particular situation – that is, whether the risk reduction for the payer is sufficient for the cost to be considered reasonable. We can say from a theoretical perspective that the longer the contract length and the higher the proportion of later payments, the greater the risk reduction achieved. However, without more advanced analysis via a health economic model for the medicine in question, we cannot say whether the contract length is long enough to provide a reasonable ICER. Nor can we say without further analysis whether payment should be conditional on whether the patient is still alive or whether it should be conditional on, for example, whether the patient begin use of another expensive medicine.

2.5.4 Being able to measure the effect of treatment is crucial for the use of outcome-based payment models

In the theoretical discussion above, we have assumed that it is possible to continuously measure – to capture with data – how good the effect of the ATMP treatment is. The purpose of focusing on the theoretical here is that the more practical implementation questions are discussed in other contexts, while we believe that the question of how much risk reduction is actually achieved by different payment models has received less attention. However, we would like to conclude with a discussion of the data. In practice, the ability to measure the impact of an ATMP treatment will be perhaps the biggest challenge of implementing

outcome-based payment models and will determine whether it is worthwhile to use this tool.

Outcome-based payment models are often based on individual data. This means that one needs to be able to track which individuals have received treatment and what health outcomes are realised. The health outcomes linked to the payment model need to be monitored within the contract period. Although there are no theoretical limits to the duration of the contract, there are practical advantages in not having contracts that are too long (the previous report mentioned 5 years (1)). This means that health outcomes, or surrogate variables for health outcomes, need to be realised within the contract period.

Outcome data must be available to all parties to the contract; not only payers but also the company with which the cost is to be settled. This is to enable both parties to meet and ensure their contractual obligations. Currently, only health data registries can guarantee access to all parties. Other registers, such as quality registers, are voluntary for both patients and health professionals to take part in. Basing outcome-based payment models on medical record data is risky, as it cannot be guaranteed that all stakeholders have access to the data or that it is possible to follow a patient across regional borders when different medical record systems are used.

When settling an outcome-based contract, the first thing to know is who received a product. The ATMPs that have been approved so far or will be approved in the coming years will all be requisitioned medicines, i.e. medicines administered in hospitals, as opposed to prescription medicines that are taken by the patient him/herself. However, there is currently no register to record which requisitioned medicines are given to which patients. However, TLV has previously shown that the patient register at the National Board of Health and Welfare could be used for this purpose (6). If requisitioned medicines are automatically registered through an ATC code, it would be possible to know which individual has received which product. It would then be possible to link different health outcomes to the start of treatment via the personal identity number.

In addition, the outcome measure needs to be relevant. It must represent a health outcome related to the effect of interest. The outcome measure should also be one that is used or generated in clinical practice. It is not desirable for a patient to have to come for repeated measurements simply for settlement of a payment model. Similarly, it is desirable that the outcome measure does not include a subjective assessment. If the payment to be made is dependent on a subjectively assessed outcome, this may be suspected of influencing the assessment.
The outcome measure should also be included in a health data register. According to TLV, the most appropriate register at present is that of the National Board of Health and Welfare.

An additional aspect that needs to be addressed is patient confidentiality. An outcome measure will in all likelihood include information on the health status of the patient. Before sensitive data is shared, it must be ensured that no data is made available to staff who are not authorised to handle it. These are aspects that this report does not intend to address, but they are factors that must be considered before a contract is entered into.

3 Opportunities to support the development and use of new payment models

3.1 Developing the use of payment models to increase access to medicines

3.1.1 TLV is responsible for carrying out health economic assessments of in-patient medicines

TLV currently carries out health economic assessments of certain in-patient medicines on the basis of the Decree (2007:1206) with instructions for the Dental and Pharmaceutical Benefits Agency, i.e. TLV's instructions. It is the NT Council that initiates which in-patient medicines and which indications TLV will evaluate. Within the framework of what is known as the in-patient medicines mandate, TLV prepares information for the regions prior to their purchase of medicines.

If the regions find that the cost of the in-patient medicinein question exceeds the regions' willingness to pay, based on TLV's health economic assessment, the NT Council can issue a negotiating mandate. The aim of the negotiation with the company is to obtain conditions for the regions that allow the treatment to be assessed as cost-effective. At present, this is usually done through a managed entry agreement, whereby the company reimburses the regions for part of the cost of the officially quoted price of a medicine. If the outcome of the negotiation with the company is acceptable in terms of the regions' willingness to pay, the NT Council can make a recommendation to the regions to use the medicine. Subsequently, all regions can sign a contract with the company (7).

3.1.2 Outcome-based payment models may in some cases be more appropriate than contracts based on straight discounts

There are different forms of payment models, such as outcome-based models and straight discounts. A straight discount is a simpler form of contract in which the payer and the company agree on a percentage straight rebate that reduces the cost of using the medicine. Straight discounts may not be the most efficient way of handling the large uncertainties associated with, inter alia, the long-term effects of ATMPs. Ultimately, if the payer (public authority) and the pharmaceutical company do not agree on what is a reasonable cost, there is a risk that the treatment will not be available to the patient.

However, an agreement between the payer and the pharmaceutical on a payment model reducing the payers risk can make the treatment available to patients. For example, such a payment model may mean that the payment for the medicine is not a constant sum per pack but varies based on health outcome, indication for which it used, volume purchased or other factor.

3.1.3 TLV has analysed how it can support the use of payment models for ATMPs

In the previous government mandated report, TLV conducted a broad analysis of the need for and the possibilities of developing and using payment models. TLV concluded for instance that that outcome-based payment models should be explored for ATMPs, where payment is made based on actual realised benefit from the treatment (1).

Current work has focused on what TLV as an authority can develop to promote the use of payment models.

In the context of the current mandate, TLV has developed methods to demonstrate the risk reduction that a payment model can provide. TLV has also initiated the development of a simulation tool that can be used to gain more knowledge about the appropriateness of a particular payment model. It is expected that such a tool could be helpful for regions and companies in the event of a negotiation on an actual payment models. This work is presented in Chapter 2.

In this chapter, TLV presents proposals on how TLV can support the use of payment models in actual assessments of in-patient medicines. ATMPs are essentially in-patient medicines, since they require the assistance or supervision of healthcare professionals and are administered in hospitals. The following reasoning therefore applies only to in-patient medicines for which TLV carries out health economic assessments.

The corresponding handling for reimbursed medicines, where TLV makes decisions on price and subsidy according to the Pharmaceutical Benefits Act (2002:160), would require further considerations and is not examined in the context of this report.

3.1.4 There are practical challenges with the implementation of payment models – these are not explored further in this work

In this analysis, TLV does not describe and consider some of the practical prerequisites for payment models to work in practice, such as access to data of relevant outcomes on which to base payment. However, we would like to stress that there are a number of challenges related to this. Section 2.3.5 provides a review of some of these. The report from the previous government mandate also contains an account of important prerequisites for payment models in a Swedish context (1).

This report also does not consider the legal conditions for regions to enter into long-term contracts, for example. With regard to the duration of contracts, according to the Local Government Act (2017:25) [kommunallagen (2017:25)], municipalities and regions must have good financial management, which means, among other things, that revenues cover current expenditure. The cost of medicines falls under current operating costs, and treatments with very high prices thus risk generating a financial imbalance in the regions (8).

3.2 Different ways in which TLV could potentially support the use of payment models

3.2.1 Legal basis for TLV to support the development and use of payment models

Payment models can be discussed from both theoretical and practical perspectives. In a legal sense, the payment models discussed in this report consist of a set of contractual terms in a civil law agreement negotiated between a pharmaceutical company and one or more regions. The TLV is not a party to such an agreement.

There are a number of general provisions governing TLV's activities. The following are the most central provisions that may be relevant to the questions addressed in this report. An authority may only take measures that are supported by the legal framework and must therefore have a statutory basis for its administration and case management[3]. Administrative authorities must respect the equality of all before the law and observe impartiality in their activities, which includes requirements of equal treatment and objectivity[4]. The requirement of objectivity is given concrete form by other provisions, such as the provisions on conflict of interest in the Administrative Procedure Act [förvaltningslagen], which aim to avoid conflicts of interest that might call into question the objectivity of a representative of an authority. Public authorities also have an obligation to help individuals to safeguard their interests, referred to as the duty of service[5]. Assistance must be given to the extent appropriate to the nature of the matter, the individual's need for help and the activities of the authority. Thus, public authorities must offer service and some advising, but only to the extent that objectivity cannot be called into question because the duty to provide service is subordinate to the requirement of impartiality. The assistance offered by a public authority must therefore not go beyond what is covered by the concepts of advising and service. These circumstances must be taken into account in all its activities, including health economic assessments of in-patient medicines.

In its instructions, TLV's current mandate regarding in-patient medicines is worded as follows: "*The Agency shall carry out health economic assessments of medicines and medical devices that are not included in the pharmaceutical benefits scheme and that are requisitioned for inpatient care or procured by the regions"*[6]. There are no additional provisions regarding this handling; the general provisions of, for example, the Administrative Procedure Act (2017:900) and the Public Access to Information and Secrecy Act (2009:400) [offentlighets- och sekretesslagen (2009:400)] are applicable to the handling of the matter.

3.2.2 TLV can evaluate and develop proposals for payment models

Below, TLV outlines a proposal for how the Agency could support the development of payment models in the context of TLV's health economic assessments of in-patient medicines, such as ATMPs. We also discuss how

[3] Chapter 1, § 1 of the Instrument of Government [regeringsformen] and § 5, Paragraph 1 of the Administrative Procedure Act (2017:900) [förvaltningslagen (2017:900)]
[4] Chapter 1, § 9 of the Instrument of Government and § 5 of the Administrative Procedure Act (2017:900)
[5] § 6 of the Administrative Procedure Act (2017:900)
[6] § 2 of the Decree (2007:1206) with instructions for the Dental and Pharmaceutical Benefits Agency [förordningen (2007:1206) med instruktion för Tandvårds- och läkemedelsförmånsverket]

the proposal relates to the legal framework and other aspects to be considered before the possible introduction of such an approach.

Where TLV has conducted a health economic assessment of an in-patient medicine, TLV has extensive knowledge and information about both the clinical and health economic evidence, including the uncertainties that may exist about the cost-effectiveness. Pharmaceutical companies are now expressing a willingness to discuss payment model proposals (i.e. contractual terms) with TLV and the regions in certain cases. Today, negotiations on payment models are conducted between the regions and the company after TLV has finalised the health economic evaluation. TLV is therefore not usually involved in these discussions.

In order to best support the development of payment models, TLV believes that the Agency should develop proposals for payment models in connection with the health economic assessments by, inter alia, identifying and proposing important components to be addressed in such a model. This could then form the basis for more complex contractual structures. Such a process would include an evaluation of how the negotiating parties' proposed payment model addresses the key uncertainties and how it affects cost-effectiveness, as well as an evaluation of proposed outcome measures and the possibility of monitoring them. If relevant to the specific case, TLV should also suggest how the current payment models could be adjusted to be more appropriate in terms of achieving sufficient risk reduction. In some situations, it is also conceivable that the initial proposal for the appropriate payment model is mainly developed by TLV and not by the negotiating parties.

The aim of this approach is to give both the companies and the NT Council and regions a better opportunity to come up with a contractual solution that is adapted to the conditions of the product in question. An evaluation of the payment model proposal facilitates the final negotiations, as both parties are given an enhanced opportunity to assess the impact of the payment model and the final cost-effectiveness.

In order for TLV to evaluate the impact of a specific payment model on the cost-effectiveness of a medicine, such analyses need to be possible in the health economic model developed by the company in the context of the health economic evaluation.

As mentioned above, TLV needs the support of the legal framework for its actions. Furthermore, the TLV may not base its decisions on considerations other than those which the applicable regulatory framework allows to be taken into account in the examination of a case. TLV mean that it is questionable whether the development of payment models and other contractual terms is part of TLV's current mandate to perform health economic assessments of in-patient medicines. For reasons of transparency and based on various aspects of legal compliance, such as the principle of legality and the principle of equal treatment, we therefore judge that this mandate needs to be included in TLV's instructions, i.e. the Decree (2007:1206) with instructions for the Dental and Pharmaceutical Benefits Agency. TLV therefore proposes a change in the Decree to

make clarify that, for in-patient medicines, TLV may evaluate and develop proposals for payment models that can form the basis for a contract between regions and companies and also develop drafts of such contracts. A consequential amendment to the Public Access to Information and Secrecy Regulation (2009:641) [offentlighets- och sekretessförordningen (2009:641)] is therefore also needed so that confidentiality also applies to this new information.

TLV's health economic assessment is summarised in an evidence base that is sent to the NT Council, which can then make a recommendation to the regions based, among other things, on the TLV's health economic assessment. It is the NT Council that initiates any negotiations with the company, with the aim of obtaining terms for the regions that allow the treatment to be deemed cost-effective, but it is the regions that sign contracts with the company.

For the proposed approach to be possible, TLV and the NT Council need to be able to exchange information with each other, including during the handling of the case. For example, TLV would need to share assessments of the company's health economic model, assumptions in the health economic evaluation, and appropriate and possible outcome measures that can be monitored for the proposed payment model. In order for TLV to assess risk reduction for a particular payment model, TLV would need to receive information on what is being discussed in the negotiations. The above is information that is or would be held by TLV and in many cases is deemed to be sensitive information, where companies could be expected to suffer harm if the information is disclosed. There is no confidentiality provision giving the NT Council the right to access sensitive information. TLV can therefore only share information if the company agrees to waive confidentiality on the basis of Chapter 12, § 2, Paragraph 1 of the Public Access to Information and Secrecy Act. Under the current procedure for the evaluation of in-patient medicines, companies are asked for such a waiver of confidentiality. This is not a satisfactory arrangement and the TLV has pointed out this shortcoming previously. TLV therefore continues to see a need for the procedure to be reviewed and regulated.

A further prerequisite for the proposed approach is that there is a mutual interest between the contracting parties to negotiate a possible payment model, i.e. that both parties intend to enter into a contract with a more complex structure. Thus, all companies are given the opportunity for proposed management, but it is up to the contracting parties jointly to decide whether TLV should evaluate a payment model before or during negotiations. Thus, TLV does not make a selection as to in which cases this will take place.

Another aspect that needs to be taken into account is the additional time that the proposed approach would entail. A procedure in which companies and the NT Council negotiate on the basis of the health economic assessment made by TLV and then submit a basis for a payment model that TLV will finally evaluate is an approach that takes some time. There is no specifically regulated turnaround time for in-patient medicines in the same way as for reimbursed medicines, but TLV currently has a target of 120 days. The proposed new procedure is likely to increase the processing time. In TLV's view, it is difficult to predict whether the processing proposed here will fit within these timeframes.

In addition, such an approach would require increased resources at TLV – in terms of both scope and relevant expertise. The handling requires human resources that would otherwise be used for other evaluations. Depending on the complexity of the payment model and the calculations made, evaluating the model's effectiveness may be more or less resource-intensive.

In the context of this work, TLV has not explored in detail the process of the proposed approach. For example, at which stage of the investigation TLV identifies and proposes components of a payment model needs to be considered.

3.2.3 In addition, TLV could develop a number of standardised payment models that could be applied to ATMPs

TLV also believes that there could be benefits in developing a number of standardised outcome-based payment models that are deemed capable of managing uncertainties and reducing payer financial risk in a number of situations, and that could be used in contracts between companies and regions in relation to ATMPs.

As reported in Chapter 2, TLV has begun the development of a simulation tool to calculate the risk reduction that an outcome-based payment model can provide. In its current form, it is primarily intended as an educational tool to understand, for stylised hypothetical conditions and treatments, the main mechanisms involved. TLV sees value in further developing the tool for possible use in actual evaluations. For this to be possible, the tool must allow for detailed description of the health condition. Such a description could be close to the health economic models that companies submit to the TLV. The tool could also be used for other types of treatments than ATMPs.

At present, TLV has not identified any legal obstacles to the development of such a tool.

3.2.4 The importance of continued collaboration with the regions

During the period of the previous government mandate, TLV established collaboration with the regions in the context of a pilot project. The aim was to investigate the possibilities for developed payment model(s) that are economically, practically and long-term sustainable for Swedish conditions. The work of the regions in the pilot project was based on the development mandate of the Swedish Association of Local Authorities and Regions (SKR) to review the possibilities of developing new contractual structures and payment models (9).

Both TLV and the regions see great value in continuing and developing this collaboration. TLV sees a need for a well-functioning structure for national collaboration on these matters.

4 Whether the total usage of a medicine should influence the cost accepted

4.1 TLV weighs cost against health gain and severity

The method used by the TLV and the NT Council to determine whether the cost of a medicine is reasonable is often referred to as value-based pricing: the greater the health gain of a medicine, the higher the cost accepted. The maximum price of a medicine is thus determined based on its value to the average patient. Value-based pricing in its purest form means that sales volume, sales value or budget impact do not affect the accepted price.[7]

TLV is working continuously to develop value-based pricing. Among other things, for a number of years TLV has allowed patient numbers, in combination with other criteria, to influence the accepted cost in certain cases. However, the question of whether small patient numbers and sales volumes should be taken into account to a greater extent in TLV decisions has become even more relevant in recent years due to the increasing number of new medicines targeting small patient populations, such as precision medicine, with increasingly higher prices. TLV therefore finds it imperative to investigate further whether it is reasonable to expand the application of the rarity of the condition affecting the cost that is accepted – to set lower cost-effectiveness requirements for rarity. At the same time, TLV sees a case for investigating whether it is reasonable to impose higher cost-effectiveness requirements for high-selling medicines and, if so, how this could be applied.

4.1.1 Value-based pricing is in many cases a workable model for regulating pharmaceutical prices

The value-based pricing model works well in many ways for the pricing of medicines. The principle that the cost of an intervention should not exceed its benefit is justified by the need to use society's resources where they can do the most good. Cost-effectiveness analyses of medicines therefore have their counterpart in the socioeconomic calculations that are made, for example, for investments in infrastructure. If the principle is applied categorically and consistently, the public will – at least in theory – pay the same amount for the same health gain, regardless of the disease and treatment.

However, since TLV applies different limits to what is considered a reasonable cost depending on the severity of the disease, medicines for more severe conditions may

[7] This is the case as long as average health gain is not affected as use increases, for example if use is expanded to patient groups with less patient benefit or lower severity.

cost more in relation to the health gain. This is in line with the needs-solidarity principle in healthcare's ethics platform, which implies that severe diseases should be given priority over less severe ones. This means that society pays more for a given health gain, the more severe the disease.

Value-based pricing provides clear incentives for companies to develop new effective medicines, as the greater the health gain, the higher the price accepted. However, the fact that the principle provides incentives for the development of effective medicines is not usually cited as the main reason for applying value-based pricing, but is a side effect; see e.g. SOU 2017:87 (10).

However, the incentives are not optimal in the sense that the price accepted is perfectly tailored to the strength of the “signal” needed for companies to develop products for a particular disease. One reason is that companies' revenues depend not only on price but also on sales volume, which, as mentioned earlier, is not taken into account in value-based pricing. Therefore, in order for incentives to be equally strong, the price of medicines targeting small patient groups may need to be higher than for medicines targeting large patient groups.

The implication of this is not necessarily that an authority such as TLV should seek to provide *optimal* incentives for the development of medicines. This is a difficult task, which may also conflict with other healthcare objectives. However, even if optimal incentives are too ambitious a goal, there may be scope for improved incentives.

This chapter is not an exhaustive examination of whether TLV's practice in this regard should be changed. Rather, the chapter is intended as an introduction to the discussion – as we understand it. However, TLV believes that an investigation should be undertaken. Is there a case for allowing volume – i.e. how *large* or *small* the expected and actual use of a medicine is – to play a greater role in TLV's decision-making?

4.2 Accepting higher costs for medicines for rare conditions

There is a practice at TLV to accept a higher cost per health gain achieved in some cases

In a number of cases, TLV has taken into account the fact that a treatment is targeted at a rare condition by accepting a higher cost per health gain than is normally accepted (see e.g. TLV decision no. 1967/2015 (11)), based in part on the conclusions of a report by the National Centre for Priorities in Health in an annex to the Pharmaceutical and Pharmacy Inquiry [Läkemedels- och Apoteksutredningen] (SOU 2014:87) (12). The authors argue that the healthcare ethics platform provides an opportunity to take special considerations into account when prioritising medicines targeted at rare and very severe conditions – this is because patients affected by rare

diseases are then given more equal access to health-improving treatments compared to other patients.[8]

In the report, the authors set four conditions for accepting a higher cost per health gain:

- that the treatment has a high cost per health gain as a consequence of it involving only a small number of patients,
- it relates to a condition of very high severity,
- the treatment option under consideration is reasonably expected to have a significant effect,
- there is no alternative treatment with a significant effect that is expected to prevent.

The report does not take a position on *how* much more it is reasonable to pay for rare conditions, but stresses that there must be an upper limit to the cost per health gain that society can accept even for these medicines.

The report also discusses how rare a condition should be in order to qualify for the higher accepted cost per health gain. The authors argue that the cut-off should be set considerably lower than the accepted definition of orphan medicinal products and that, for Sweden, a discussion could suitably be based on the assumption that the expected size of the patient group should not exceed 200 patients (1 in 50,000 inhabitants) over five years.

In the remainder of this section, we provide a somewhat broader introduction to the issue of rarity and higher willingness to pay.

4.2.1 Arguments put forward for accepting higher costs for medicines for rare conditions,

"Companies need sufficient incentives to develop new medicines"

Pharmaceutical companies' costs are mainly fixed, in the form of research and development (R&D) expenditure. Variable production costs are often a smaller part. Although fixed costs are lower for medicines for small patient populations than they are for large populations (13), they are still so high that the R&D cost per patient treated is higher for medicines in small patient populations. Therefore, according to this argument, if price regulators do not take this into account, the expected profitability and the willingness to invest in the development of medicines for small populations may be hampered. According to this view, we should therefore pay more for current medicines for rare conditions in order to provide incentives for the development of future medicines for rare conditions.

TLV interprets this argument as being in line with the first condition set by the Priority Review Centre for what must be the case for a higher cost per health gain to be acceptable – "that the treatment has a high cost per health gain as a consequence of it involving only a small number of patients". This

[8] The wording of the annex is: "*given greater equality of access to health compared to other patients*".

is because it is difficult to see any reason, other than the higher R&D cost per patient, why a medicine for a rare condition must be priced higher than medicines targeting larger patient groups.

An important extension of this argument is that the price of a medicine often falls over time, especially at patent expiry. So, even if the price accepted during the patent period may be considered too high, i.e. does not provide sufficient health gain in relation to the cost of treatment, it may do so in the longer term. However, one objection to this is that it applies to all medicines, not just those for rare diseases. In fact, it probably applies to a lesser extent to rare conditions because competition is often weak for medicines targeting small populations after patent expiry and the price therefore falls to a lesser extent. Should TLV therefore, for all new medicines, accept prices above a cost-effective level for some time?
The answer is that for most medicines we do not need to accept poor cost-effectiveness in the short term for there to be sufficient incentives to develop them. It would also lead to excessive inefficiencies in healthcare if medicines were to be introduced on a regular basis despite the fact that the cost of treatment is unjustifiably high.

In summary, the incentive argument can be described as: for medicines targeting rare conditions, we may have to accept costs that are "too high" for a number of years for there to be an incentive to develop them, and yet looking further ahead, they may hopefully deliver sufficient health gains to justify the cost as the price is expected to be lower in the future.

TLV finds some validity in this argument, which is a main reason why it has set lower cost-effectiveness requirements, i.e. accepted a higher cost per QALY gained, for a number of medicines for very rare conditions.

"Current evaluation methods miss a large part of the value"

Another argument that has been put forward for the inclusion of patient numbers in the decision is that the health economic methods used are not able to capture the full *value* of treatments for rare diseases (14). According to this argument, TLV and other corresponding authorities therefore overestimate the actual cost per QALY gained. In other words, if TLV were able to capture the full value, the cost per QALY gained would not be as high.

TLV sees this as a weaker argument for accepting a higher cost per QALY. If the value of these medicines is not captured accurately today, it is more an argument for developing better methods to measure the value.

"Sweden must adapt to the price level that has been established internationally"

The prices that companies set for their new medicines do not vary much between Western European countries, especially at the time of introduction (15). This is particularly true of official prices, but probably also of the confidential so-called net prices. Therefore, if other countries accept high prices for medicines

for rare conditions and companies are not able to adjust prices to the level accepted in Sweden, the medicines will not be available here.

Whether access to medicines for rare conditions (orphan medicinal products) is worse in Sweden than in other Western European countries is a complex question that cannot be answered easily (16). It is also not the question we address here. Instead, we ask the principal question of whether Sweden should depart from the value-based pricing model and instead accept the Western European price level and make the medicine available – whether or not the cost can be justified based on TLV's current practice.

This is not an argument that TLV has used so far to justify the higher accepted cost of medicines for rare conditions. Again, we cannot take a position on the reasonableness of the approach, but note that there may be quite far-reaching consequences if the price accepted in Sweden is not based on health gain but on the prices accepted in other countries – if indeed other countries accept higher prices for rare medicines than we do in Sweden.

4.2.2 What should influence how much higher a cost is accepted?

The number of patients presenting for treatment is the variable that has often been used in the debate as an indicator of whether a medicine is targeting a rare condition, and where the R&D cost per patient is therefore high. TLV has judged this to be a relatively good measure, although not without weaknesses. Further investigation of what is the best measure is therefore required.

There is also an argument that the actual development cost of the specific medicine should influence the accepted price (17). Not all medicines for rare conditions have had high development costs. However, TLV argues that it is generally inappropriate to let the R&D cost of the specific medicine influence the price.
This is for two reasons. Firstly, it is hardly possible to determine in a fair way what the R&D cost was. For example, how can the costs of all failed projects be captured? Secondly, even if the R&D cost could be determined, it is questionable whether this is appropriate, since an important reason for allowing rarity to have an impact, according to TLV, is to provide incentives for the development of future medicines: how can society send a signal via price about the type of R&D considers important?

This should not be interpreted as meaning that it is irrelevant to take costs and profitability into account altogether. For example, what might be considered is what the average development costs are for different types of medicines. Here, as mentioned above, there is evidence that products for small populations cost less to develop on average than products for more common conditions.

There is a case for investigating whether a clearer link should be made between accepted ICER and patient number

The purpose of this chapter is thus not to provide a detailed discussion on the application of higher willingness to pay in rare conditions, but rather to

conclude that a broader investigation is needed. Should the current application be changed in any way? Some of the questions that should be answered are: What if a medicine has more than one indication, where someone is in a rare condition but the total patient population for the medicine is not small? What if it turns out that the medicine, in practice, is used by far more patients than was estimated in the reimbursement decision? How do we deal with the fact that many of the new medicines being developed are for small patient groups? How should the accepted cost per QALY increase as the number of patients gets smaller?

4.3 Setting higher cost-effectiveness requirements for medicines with high sales volumes

Accepting a higher cost per QALY for medicines targeting small patient populations can be expressed as a lower cost-effectiveness requirement for this type of medicine. Should we then set higher cost-effectiveness requirements than today for medicines with high sales volumes? The theoretical arguments for and against this should be explored in parallel with the question of higher acceptable cost for medicines in small patient populations: How should the public think about incentives for the development of future medicines for common conditions in relation to society's need to create immediate benefit – benefit for today's patients – for the available resources?

Setting higher cost-effectiveness requirements can be implemented in different ways, for example:

- Accepting lower cost per QALY than today at the time of decision-making.
- Requiring higher levels of cost-effectiveness actually demonstrated in clinical practice after the medicine has been used for a number of years.

There are also other possibilities. For example, some countries take into account the budgetary impact of introducing a new medicine (18)[9].

The arguments for accepting a lower cost per QALY than at present at the time of decision-making largely mirror the arguments we discussed for paying more for small patient populations.

The arguments for requiring higher levels of actual demonstrated cost-effectiveness in clinical practice are based on the fact that TLV usually conducts evaluations when medicines are new and not yet used in clinical practice. However, efficacy and use in clinical practice may look very different from that initially assumed by TLV in its evaluation: efficacy may turn out to be worse or better, and the patients who use the medicine may have different characteristics. Monitoring efficacy and use and adjusting the price based on the results has therefore long been an objective of both companies and TLV. However, it has proven to be difficult and resource-intensive, and has therefore not been done to a sufficient extent. TLV has an ongoing government mandate to develop the agency's approach to this (19).

[9] See page 12 in Appendix 2

The reason for focusing more on high-selling medicines in terms of demonstrated cost-effectiveness in clinical practice is that it is most important from an overall socioeconomic perspective. Costs that are too high relative to the health gain of infrequently used medicines matter less than costs that are too high for products that are sold in large volumes.

5 Taking into account the impact of a disease and treatment on informal caregivers' quality of life

5.1 Caregivers' quality of life as an aspect of decision-making

5.1.1 Many diseases have a major impact on the patient's family members; thus, treatments may also have an impact on them as informal caregivers

In the previous report (1), TLV reviewed various value aspects that may be of particular relevance to precision medicine and ATMPs and whether there is a case for considering any of these aspects in the health economic evaluation. TLV concluded then that there is a need to further analyse and discuss these issues and suggested that the focus should first be on the issue of quality of life of informal caregivers. (In this chapter we use *family members* and *informal caregivers'* interchangeably, but the meaning is the same) However, this is a matter that is not limited to ATMPs or precision medicine.

The impact of a disease on the quality of life of family members – and whether a health economic evaluation of a treatment should take into account that the quality of life of family members may improve if the patient's condition improves – is probably one of the most debated value aspects in recent years. The aim of this investigation has been to analyse whether it is justified to take this value aspect into account in TLV's decision-making and, if so, how this can be done.

As part of this investigation, TLV commissioned a research group from the Karolinska Institute to write a report on the matter (2).

The research group based its work on the following questions:

- What external effects on relatives[10] may occur as a result of different healthcare interventions?
- What are the arguments for and against taking effects on informal caregivers' into account when deciding on reimbursement of a medicine?
- How can effects on informal caregivers' be taken into account in decisions on reimbursement of a medicine?
- What instruments can be used to measure effects on informal caregivers' for use in health economic evaluations?
- What are the possible consequences of taking effects on informal caregivers' into account when deciding on reimbursement of a medicine?

TLV has not presented all parts here. Please refer to the supporting report for more details.

This chapter sets out TLV's views on aspects that we consider crucial to whether and how the quality of life of family members should be taken into account in our health economic evaluations and decisions. The chapter reviews the practical conditions – what effects on family members can be considered and how they can be calculated. We also discuss ethical aspects and whether there is a case for lowering the accepted threshold, i.e. the accepted cost per quality-adjusted life year, if effects on the quality of life of family members are taken into account.

5.1.2 To date, TLV has not considered the impact of a disease and a new treatment on the quality of life of the patient's family members

An individual's disease almost always affects family members in one way or another. It can affect the family members emotionally and practically through changes in family life and the need to provide informal care, and lead to poor mental health. It can also have a financial impact through the costs of care or a reduction in family income. If the disease leads to death, it means grief for the family members.

From a health economic perspective, the consequences can either be in terms of quality of life or in terms of costs. To date, TLV has not based decisions on an ICER in which quality of life effects on family members have been included. Where companies have included the effect on caregivers' quality of life in their health economic calculations, TLV has usually reported the results of this in a scenario analysis, but it has not formed the basis for the assessment of reasonable cost under the Pharmaceutical Benefits Act.

There are several challenges to including the effect on caregivers' quality of life in health economic evaluations, such as difficulties in measuring the effect (2). In several cases in which companies have included effects on caregivers' quality of life, TLV has found there to be shortcomings in the data and evidence used by the applicant companies to quantify the net gain to the patients' family members[11]. In addition, there are uncertainties and challenges regarding the methodology of how to include caregivers' quality of life in the effect of a medicine, for example how to take caregivers' quality of life into account if the patient dies (2). Another aspect is that healthcare resources are limited and priorities have to be set. Paying for caregivers' quality of life gains will result in fewer resources being available to create health gains for patients. This means that by including a quality of life gain for family members, there is a risk of prioritising diseases that affect people who are likely to have more family members in general. This may be considered contrary to the human dignity principle of the ethics platform, which states that all people have the right to the same care regardless of, for example, social status or age (20). Below, we further discuss these aspects.

[11] Supporting documents for decisions in the cases ref. no. 1963/2019, ref. no. 1877/2019, ref. no. 1076/2020, ref. no. 1961/2015; available at tlv.se.

5.1 Practical conditions and key principles to consider when taking this aspect into account

5.1.1 There are different proposed approaches to include caregivers' quality of life in the health economic evaluation

Based on TLV's experience, data on the magnitude of effect that a treatment has on caregivers' quality of life are usually very uncertain. In addition, there is methodological uncertainty about how and when caregivers' quality of life should be included in the calculation of ICERs. A review of health economic evaluations performed by NICE up to January 2019 confirms TLV's assessment (21). The review found that carer's/caregivers' quality of life has only been included in 16 out of a total 422 published evaluations. Furthermore, the study shows that there is no consistent way in which different companies include this effect, neither in terms of which disease states nor in terms of choice of method.

The lack of a systematic way to include caregivers' quality of life could potentially lead to increased uncertainty in health economic calculations. This, in turn, could potentially lead to improper prioritisation and allocation of healthcare resources. Thus, if caregivers' quality of life is to be included in the calculations, it needs to be done in a way that minimises the risk of introducing a level of uncertainty in the calculations on which reimbursement decisions are based.

Heintz, et al. (2) report on methods found in the health economics literature for including informal caregivers' quality of life. These are briefly presented below.

The additive model

In an additive model, the effect is included by calculating the QALY gain of the family members separately and then adding it to the QALY gain of the patient. This method does not make any assumption about the QALY gain of the family members relative to that of the patient, but determines it directly by measurement. Optimally, the same method should be used to measure the quality of life of both the patient and the family members.

The multiplier model

In this method, the effect is included through a multiplier effect: the patient's QALY gain is multiplied up by a certain factor to capture the effect on family members. The method requires an assumption about the relative size of the QALY gain for the family members compared to the patient.

Two multipliers are included to also adjust for the opportunity cost of including the external effects of family members. The magnitude of the two multiplier effects needs to be estimated for the two treatments.

Multicriteria analysis

In a multicriteria analysis, caregivers' quality of life is not captured in the calculated ICER, but is instead added as a separate decision criterion, as TLV currently does with severity, for example. If the effect on family members is large, a higher ICER would be accepted.

This method indirectly increases the patient's QALY gain by a multiplier, and is thus similar to the multiplier model – but less precise. This method does not require a quantitative estimate of the magnitude of the effect on family members. However, the lack of a measure of the assumed magnitude of the effect on family members for different treatments makes it difficult to subsequently compare how this effect has influenced decisions.

TLV's assessment is that none of the above methods can be considered fully optimal, and that the main reason for this is the lack of reliable data on the magnitude of the effect that a treatment has on family members.

Applying a standardized approximation – a standard rate

TLV finds that an alternative method can be to apply a standard rate – at least for the next few years, until better methods and data are available. Figure 9 illustrates how such a standard rate can be applied based on the QALY gain that the treatment generates for the patient.

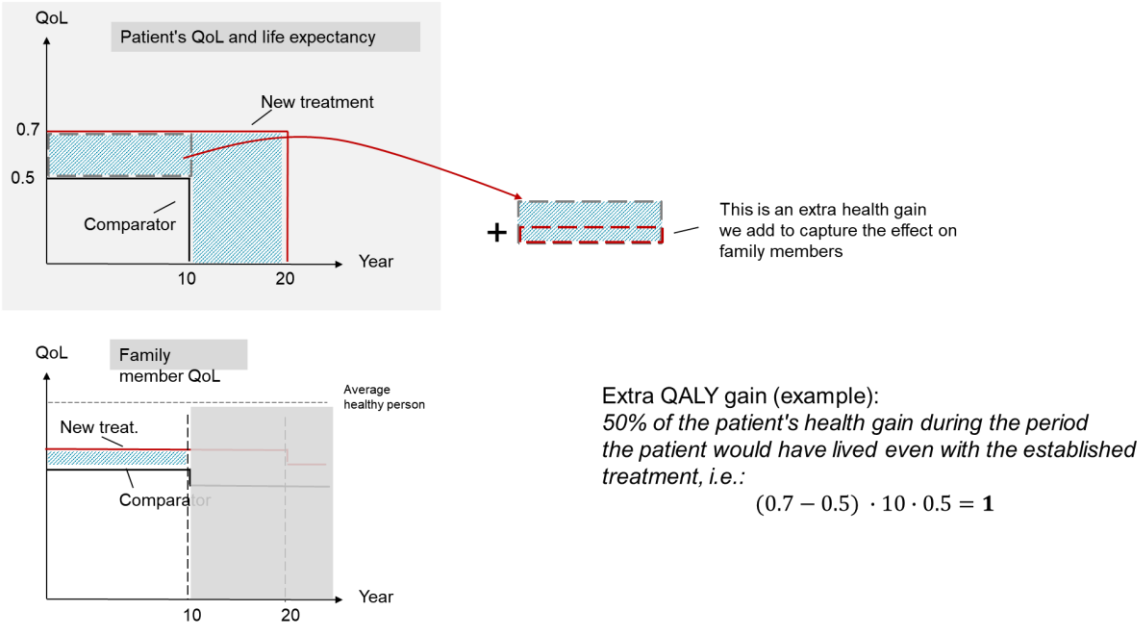


Figure 9: Illustration of how a standard rate can be applied for a treatment's effect on family members to be included in the calculation of ICER

In order for TLV to accept the application of a standard rate for a treatment, the applicant company must be able to convincingly demonstrate with data and evidence that the impact on family members is high for the condition in question (e.g. impact on daily life, living situation and health) and that the treatment can lead to an improvement in health-related quality of life for the family members.

A disadvantage of applying a standard rate in this way is that an element that is not based on actual measurements is introduced into the ICER calculation. This makes it more difficult to interpret and compare what the ICER calculation represents for different treatments, when a multiplier of the QALY gain is sometimes included and sometimes not. The magnitude of the standard rate also needs to be determined.

5.1.2 Not all effects on family members should be included

A difficult question is whether caregivers' quality of life should be taken into account during the period of increased survival that a treatment may lead to. TLV does not think so, as this could have the effect of the total QALY gain in the calculation being smaller if family effects are included versus when they are not. This is because the burden of care disappears when the patient dies. See Heintz et al (2) for a more detailed explanation of this. However, it is difficult to imagine that a treatment should be considered less essential because it prolongs life.

A further question is whether the grief of family members after the death of a loved one should be included. TLV does not think so. Family members can, of course, be greatly affected by the death of a loved one, but including this effect leads to considerations that are almost impossible to manage: How many years should the grief be assumed to last? How many mourners' quality of life should be included? Moreover, life-prolonging treatment does not mean that death and hence grief never occurs.

There are also a number of effects that tend to be addressed on the cost side for family members with a very heavy care burden, mainly reduced opportunities for gainful employment. TLV does not believe that the loss of production value for the family member should be taken into account in the decision, for the same reason the patient's loss of production value is not taken into account (1). The value of lost leisure time can sometimes be included in the calculation, but TLV argues that it would be double counting if it were included at the same time as the quality of life effect was included in QALYs gained. If family members receive tax-funded financial support as compensation for caring for a family member, this should be included in the calculation.

Who is considered a family member and for how many family members should quality of life effects be included in calculations are questions that arise in both the literature and in practice (2) (21). TLV does not consider it reasonable to take into account that different patient groups may have different numbers of family members. A possible solution is to assume effects for only one family member. In such case, there is no need for a detailed assessment of who can be considered a patient's family member. Such an assessment can also be avoided if the method of applying a standard-rate, presented above, is used.

5.1.3 The accepted threshold should not be adjusted if effects caregivers' quality of life are only considered in specific cases

Including effects on caregivers' quality of life will, in most cases, lead to a lower average calculated ICER than if this effect is not included. This will lead to a higher price for a medicine being accepted. However, changing the way we calculate does not mean that more money is available for healthcare and medicines. From this perspective, the limits on the acceptable cost per QALY gained would need to be lowered.

Thus, if the effect on family members is taken into account in a large proportion of TLV's decisions, it may be necessary to lower accepted thresholds. At present, however, TLV believes that if effects on family members are only considered restrictively – in specific cases – where there is clear evidence that a treatment leads to a health-related

quality of life gain for the family member, this should not prompt a change in accepted thresholds.

5.1.4 Taking caregivers' quality of life into account may lead to distributive effects that may be considered contrary to ethics principles

The so called ethics platform guides priority setting in all publicly funded healthcare in Sweden and consists of three guiding principles: the human dignity principle, the needs-solidarity principle, and the cost-effectiveness principle. The human dignity principle means that all people have an equal right to care, regardless of social factors such as age or social status. The needs-solidarity principle means that those with the greatest medical needs should receive more healthcare resources than other groups of patients, while the cost-effectiveness principle means that the costs of using a medicine should be reasonable from a medical, humanitarian and socioeconomic standpoint.

The New Therapies (NT) Council, which makes recommendations to the regions on the use of new medicines, has taken the position that it does not take into account the effects on caregivers' quality of life (22). This is considered to be contrary to the human dignity principle. The authors of a report by the National Centre for Priorities in Health (20), which examined ethical aspects of prioritisation, screening and introduction of medicines for Alzheimer's disease, come to a conclusion similar to that of the NT Council. The report discusses whether or not the impact on family members should be taken into account when prioritising. The report concludes that, from an ethical perspective, there are arguments both for and against considering the impact on caregivers' quality of life when prioritising, but that according to the Swedish ethics platform as a whole it is not possible to consider this aspect. This is because it can be "*...potentially discriminatory against people with few or no family members, who are then at risk of receiving poorer care*". At the same time, the report authors note that this is a difficult issue that may need to be analysed further.

Including effect on family members in health economic evaluations on which decisions will be based will thus lead to a greater use of healthcare resources for diseases and treatments that have a greater impact on family members. One way of describing this ethical problem is that if we have two equally severe diseases with a drastic reduction in the patient's quality of life, and new treatments for the conditions have the same effect on the patient, the patient with the disease for which family members are also affected will have easier access to treatment.

The ethics platform does not allow social status to influence priorities. However, since TLV makes decisions at the group level rather than for individual patients, TLV taking caregivers' quality of life into consideration should not be seen as the patient's social status impacting the decision. Nevertheless, the fact remains that if effects on family members are taken into account, diseases that have a higher impact on family members will be prioritised over those that do not affect family members. However, the existence of an opportunity cost is an effect of all prioritisation decisions and is not unique to this situation.

5.2 There may be a case for taking caregivers' quality of life into account in certain situations

The question of whether caregivers' quality of life should be taken into account in TLV decisions and, if so, how this effect can be included in health economic evaluations is complex. There are many aspects to consider, from both a health economic and an ethical perspective.

Family members are affected by the disease of a loved one, and this effect can be very large in some cases. Thus, a treatment that has a good effect on the health of the patient may, in some cases, also have an effect on the mental and physical health of their family members. In addition, the positive effect that can be achieved on the health-related quality of life of family members by providing the patient with access to a treatment with a good effect is likely to be difficult to achieve through interventions directly targeting the family member.

TLV therefore finds that there are reasons to consider quality of life effects for family members in situations where the patient's condition leads to a significant impact on the family member's daily life and situation, and when there is evidence that reliably demonstrates how a treatment can lead to improved health-related quality of life for the family member. We believe that this is particularly true in cases of long-term chronic illness where the patient's condition may lead to an informal caregiving burden for the family member that has a significant impact on daily life, family life, employability and mental health. This should therefore be taken into account in priority-setting decisions.

However, the frequent lack of good data and a systematic way of including caregivers' quality of life could potentially lead to uncertain calculations of ICERs. This, in turn, could potentially lead to increased uncertainty in decision making and possibly incorrect prioritisation and allocation of resources in healthcare. So. if the quality of life of family members is to be included in the calculations on which TLV decisions are based, this needs to be done in a way that minimises the risk of introducing an additional level of uncertainty into the decision.

6 Concluding reflections and suggestions for next steps

The Government has tasked TLV with developing methods for health economic evaluations for products included in the concept of precision medicine and for advanced therapy payment models (ATMPs).

Many of the challenges in conducting health economic evaluations are not related to the medical or technological characteristics of the product. Most of the challenges are instead of a general nature and concern many types of medicines. One example is how uncertainties can be quantified and how they can be clearly presented in TLV's health economic evaluations, in order to provide the best possible evidence for the decision-maker.
Other challenges relate mainly to specific patient groups or therapeutic areas, such as diseases that have a major impact on caregivers' quality of life or medicines used by a small number of patients with a rare condition. A third example is how we can develop our approaches and positions to make the best use of society's resources – for example, is it reasonable to make higher demands on medicines that have been on the market for some time and are selling in high volumes? However, there are challenges in evaluation and payment that are more pronounced for ATMPs than for other medicines. We believe that in some cases this may justify special solutions. In this report, we present a number of analyses and conclusions that apply to all types of medicines, but also to a number that are specific to ATMPs.

TLV sees a need for continued ongoing development of health economic evaluation methodologies and approaches – to meet the challenges and needs we face today as an agency and as a society. Patients should have access to medicines that are effective and add value. But we also want to find ways to ensure that the public does not pay more than necessary, for example for medicines that have been on the market for a few years.

At present, TLV has limited resources to carry out such methodological development in parallel with regular case management, and we are therefore proposing increased resources to do this successfully – both for ongoing operational development and in the form of time-limited government mandates.

Below is our assessment of what, based on the areas we have investigated in this assignment, requires further work and how such work might be carried out.

6.1.1 TLV finds that a number of questions are best developed further within the context of the Agency's core activities

Some of the conclusions and assessments that TLV has reached in this work are considered by TLV to be appropriate for further development and implementation in the context of

the regular case management process, as these are directly relevant to TLV's health economic evaluations of medicines. These are:

- To continue to review how TLV quantifies and reports uncertainties in the health economic evaluations.
- To develop methods for describing and valuing a health gain lost by delaying treatment, and how this factor can play a role in decision-making.
- To continue to review possible methods for calculating effects of family member quality of life and criteria for when this effect should be taken into account in decision-making
- To apply the methodology for calculating ICERs for ATMPs by reflecting that there are different probabilities of the duration of the effect.

TLV aims to continue the work it has begun to develop a simulation tool that can be used to improve understanding of how different payment models affect, inter alia, cost-effectiveness and payer risk in relation to ATMPs.

6.1.2 TLV proposes that the Agency be given an expanded mandate for in-patient medicines

TLV believes that the Agency has the necessary expertise to strengthen the conditions for enabling the use of outcome-based payment models, which will ultimately result in the medicines in question being made available to patients. This can be done by supporting regions and companies in evaluating and developing proposals for payment models in specific cases.

TLV's assessment is that it is questionable whether the development of payment models and other contractual terms is part of TLV's current mandate to perform health economic assessments of in-patient medicines. For reasons of transparency and based on various aspects of legal compliance, such as the principle of legality and the principle of equal treatment, TLV therefore judges that this mandate needs to be included in TLV's instructions, i.e. the Decree (2007:1206) with instructions for the Dental and Pharmaceutical Benefits Agency. TLV therefore proposes an amendment to the Decree to clarify that, for in-patient medicines, TLV may evaluate and develop proposals for payment models that can form the basis for a contract between regions and companies and also develop drafts of such contracts. A consequential amendment to the Public Access to Information and Secrecy Regulation (2009:641) [offentlighets- och sekretessförordningen (2009:641)] is therefore also needed so that confidentiality also applies to this new information.

6.1.3 TLV believes that some areas are best investigated further within renewed government mandates

TLV's work has identified a number of areas that we believe are best addressed within the framework of renewed government mandates. This is because they require more extensive investigations in collaboration with other actors and, in some cases, a more in-depth legal analysis.

Investigate and gain knowledge of the duration of effect of ATMPs to reduce uncertainties in health economic evaluations

Increased knowledge of the duration of effect of ATMPs can reduce uncertainties in the evaluations performed by TLV. TLV proposes a new mandate to improve the evidence base for health economic evaluations on assumptions about the duration of effect, based on the clinical evidence available on ATMPs and the technologies on which they are based. Such a mandate should be carried out in collaboration with researchers and clinicians in the field.

Investigate how a natural structure for collaboration on outcome-based payment models could be structured

Outcome-based payment models can be part of the solution to enable access to new innovative treatments in cases where there is high uncertainty about the expected benefit. The development of payment models needs to be done in collaboration with the regions and taking current practical conditions into account. In the previous report, TLV identified some key areas that need to be strengthened to make the use of payment models in a Swedish context feasible. One of these is how national collaboration can be built up so that negotiation, contracting and monitoring of payment models can be carried out in an appropriate and resource-efficient manner. This is an issue that TLV has not investigated in this mandate. We propose that TLV be given a renewed government mandate focusing on possible national structures that can provide stronger conditions for the development and use of outcome-based payment models for in-patient medicines, such as ATMPs.

Investigate how volume can have a greater impact on the pricing of medicines

TLV finds that there is a case for initiating an investigation and discussion of whether – and if so, how – the volume of a medicine's use should influence the requirements for cost-effectiveness, i.e. how high a cost per health gain is acceptable. This should be done from two main perspectives. The first is whether a higher cost per benefit should be accepted for products targeting small patient populations or rare conditions. The second is whether higher cost-effectiveness requirements should be set for products with high sales, in the form of either lower accepted ICERs when the medicine is new, or higher requirements for evidence from Swedish clinical practice when the medicine has been used for a number of years. At this stage, TLV has not initiated a new analysis, neither of the consequences of a change in the approach to the link between volume and pricing, nor of possible methods for how this could be conducted.

TLV suggests that such an analysis would best be undertaken in the context of a renewed government mandate to the Agency. The investigation needs to include, inter alia, an analysis of whether regulatory changes are required and what the consequences might be.

Investigate the conditions for robust processes for the evaluation, pricing and monitoring of combination medicines for cancer

In the report on the previous mandate on ATMPs and precision medicine, TLV highlighted the need for further investigation into how the evaluation, pricing and

monitoring of such medicines can best be carried out. TLV has not had the scope to investigate this issue within the current mandate. Such a mandate needs to be carried out in collaboration with the regions and the pharmaceutical industry.

6.1.4 TLV looks forward to continued work to create value for patients

Patients should have access to effective medicines – regardless of their disease or where they live in the country. As a government agency, TLV plays a central role in this work, but collaboration with other actors in the field, such as regions, patient representatives and the pharmaceutical industry, is crucial for a good outcome. TLV looks forward to working further to find forms of collaboration that both enable equitable access to medicines across the country and efficient use of our shared resources.

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Appendices

Appendix A: Calculation of probability-weighted ICER

The formula for probability-weighted ICER is:

$$Probability\ weighted\ ICER = \frac{\sum_{t=1}^{T} p_t \Delta Cost_t}{\sum_{t=1}^{T} p_t\ \Delta ICER_t}$$

Where $Cost_t$ is the difference in total costs between the new ATMP and the comparator from the time the treatment is given to year *t*; $QALY_t$ is the equivalent for the difference in QALYs and p_t is the probability of the effect disappearing in year *t*. Thus, the probability-weighted ICER is *not* a weighting of the different ICERs, as shown in Figure 10. In other words, it does not weigh the observations together along the curve. Instead, it is a probability weighting of the costs first and then a probability weighting of the QALY gains, after which the radio is calculated.

The weights, p_t, represent the probability that the effect persists until a particular year, but then disappears in that year. This probability depends on two factors:

1. The annual probability of the effect disappearing, given that it has not disappeared earlier; and
2. The probability that the effect has not disappeared in the past.

Figure 10 shows an example of the weights for the different years, p_t, with the assumption that factor
1) above is 5 per cent over the entire time period. We see that the weights decrease over time. This is a consequence of factor 2) – that the probability that the effect has already disappeared increases over time.

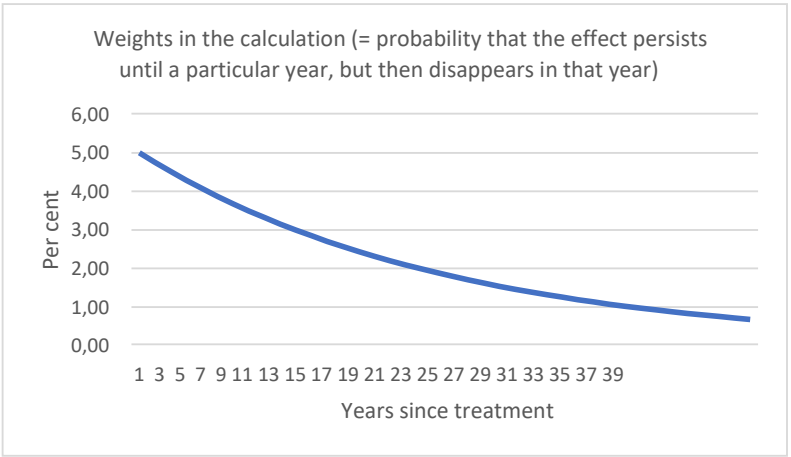

Figure 10

The probability-weighted ICER we describe here is very similar to the probabilistic sensitivity analysis discussed in Section 2.2.2.

Appendix B: A simple example to demonstrate the logic of considering the lost health gain of delaying treatment

The advantage of waiting to introduce a medicine with uncertain evidence is that it reduces the risk of non-cost-effective use. The disadvantage is that patients miss out on a potential health gain. Here we try to formalise this idea with an example to demonstrate that greater uncertainty should be accepted in cases where there is a large loss of health gain from delaying treatment.

We consider two different medical conditions, for both of which new medicines have been developed. However, at the time of the health economic evaluation, there is uncertainty about how good the medicines are. In the case of a good outcome, patients gain 10 QALYs and in the case of a poor outcome, no health gain is achieved; see Table 6. This applies to both treatments. We also assume that the cost of starting to use the medicines is the same, SEK 5 million.

The only difference between the conditions is if the treatment is not started immediately but is delayed a number of years for more evidence to become available. In the condition where medicine C is used, if it turns out that the medicine has a good effect, patients will gain fewer QALYs due to progression of the disease than if they had received treatment immediately. The lost health gain amounts to 2 QALYs (10 minus 8). However, in the condition where medicine D is used, the lost health gain is even greater, 5 QALYs (10 minus 5).

Table 6

	QALY gain			
	Condition C, where Medicine C is used		Condition D, where Medicine D is used	
	Good outcome	Poor outcome	Good outcome	Poor outcome
Treat immediately	10	0	10	0
Wait 5 years	8	0	5	0

* Net cost for both medicines is SEK 5 million.

Figure 11 and Figure 12 show graphically the lost health gain of waiting. For Condition C, there is only slow progression, while for Condition D there is rapid progression. Since the ATMP treatments for the conditions cannot restore normal health, but only delay progression, the lack of lost health from delaying treatment is greater in Example D than in Example C. The size of the grey

areas in the figures indicate the magnitude of the *lost health gain from delaying treatment*, measured in QALYs. In this example, the calculated ICER is the same for both Condition C and Condition D. The difference in *lost QALY gain from delaying treatment* is thus not reflected in the ICER calculated at the time of application.

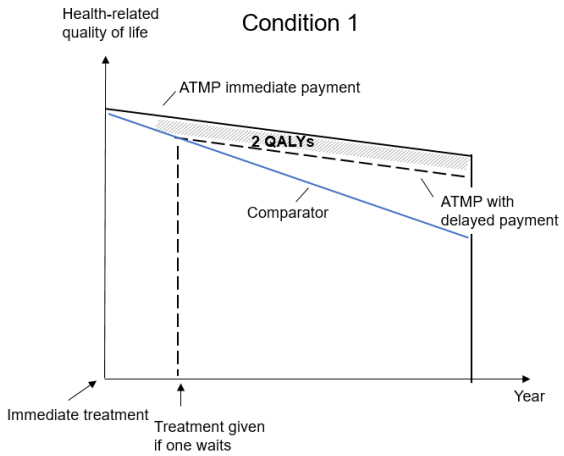

Figure 11: Illustration of health development with ATMP and established treatment for Condition 1.

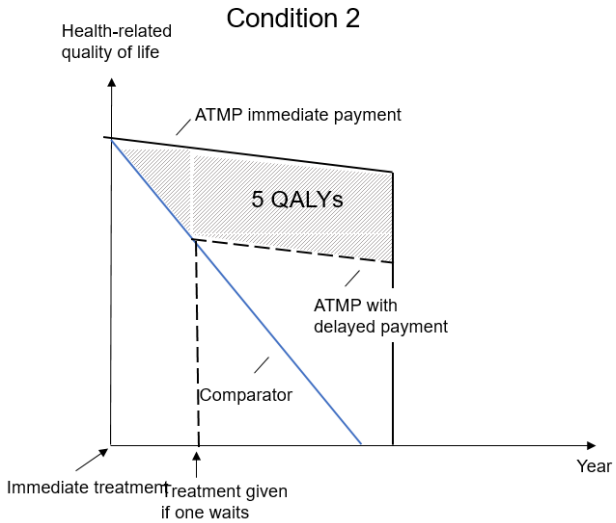

Figure 12: Illustration of health development with ATMP and established treatment for Condition 2.

The value of delaying treatment can be quantified using incremental net health benefits

The decision-maker who has to decide on medicines A and B has two choices: to allow use immediately or to wait a number of years until better evidence is available. The probability of a good outcome determines which is optimal. Figure 13 shows how the (net) value of the different decisions varies with the probability of a good outcome. The value of the different decisions can be quantified by INHB (incremental net health benefit), where the cost is converted into QALYs by putting a certain monetary value on 1 QALY, e.g. SEK 1 million.[12] In the simple example we use here for illustration, we assume that uncertainty can be completely eliminated if treatment is delayed for a number of years. The footnote shows how the value of the two strategies is calculated. (The analysis with INHB is not something we suggest TLV should use in cases. It is only used here for the purpose of analysis).

Figure 13 shows the difference in value (measured in terms of QALYs) between immediate use and delaying treatment. The higher the probability of a good outcome, the greater the value of permitting immediate treatment – an unsurprising conclusion. However, at low probability of good outcome, the difference in value is negative and the decision-maker should wait. Where the curves intersect the x-axis, the difference in value is zero, and it is possible to wait or treat immediately.

The curve related to Condition D, where there is a large health loss from waiting, intersects the x-axis at a lower probability value. The implication is that the decision-maker should accept greater uncertainty the greater the lost health gain from delaying treatment.

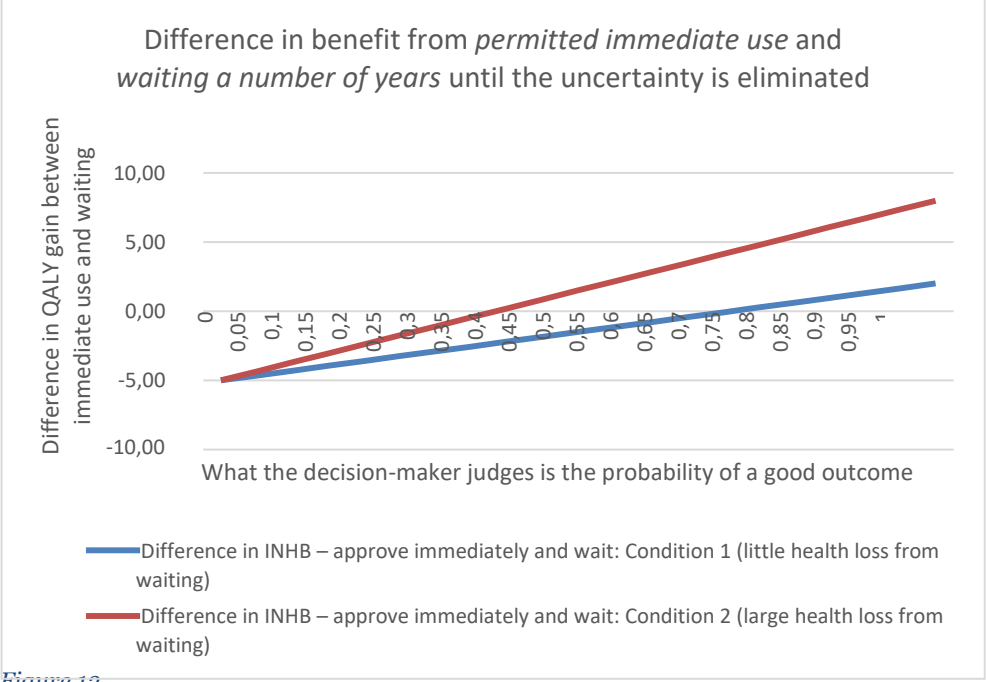

Figure 13

[12] $INHB = QALY\ \text{gain} - \frac{Net\ \text{cost}}{Monetary\ \text{value of 1}\ QALY}$.
In the example, SEK 1 million has been used as the monetary value of 1 QALY.