Policy for prioritization in the NT Council's and the MTP Council's recommendations

Summary

The mission of the NT and MTP councils is to give recommendations on the use of medicines and medical technology devices including diagnostic products respectively to the regions. All such products will be referred to in this policy as interventions. The purpose of the councils ' work is to contribute to a fair and equal access to new interventions through the effective use of limited healthcare resources.

The present policy forms an important basis for the NT and MTP councils' work in developing recommendations that can be guiding the regions. It aims to facilitate the production of informed, clear and transparent recommendations that are consistent over time. The policy also aims to increase understanding of the content of recommendations and the predictability of future recommendations. This is of great importance to patients, regions, companies, and other stakeholders.

To recommend whether and how society's resources should be used for an intervention, one needs to make an evaluation in accordance with the principles of the ethical platform: the human value principle, the need and solidarity principle and the cost-effectiveness principle.

The *human value principle* means that all people have equal value and the same right regardless of personal characteristics and functions in society. The principle is superior to the other principles and serves as a framework and clarifies which considerations that must not be taken into account when setting priorities.

The *need/solidarity principle* means that patients with the greatest needs must be given precedence before those with less need. It clarifies basic principles of equity and equality in a health care context.

The cost-effectiveness principle means that the cost must be reasonable in relation to the benefit.

Based on the nationally accepted operationalization of the platform, it implies an evaluation of and balance between: •

- the severity of the condition •
- the rarity of the condition •
- the uncertainty in clinical data and in the health economic assessment

In relation to: •

- the cost-effectiveness of the intervention (in the form of SEK/QALY[1] , ICER[2])

The balance then determines whether the price of the intervention is acceptable and can justify a recommendation in the form of “should”, “can” or “do not”. Other non-financial resources, (personnel, infrastructure) may have an impact on the recommendation, but the price is what can be affected in connection with the recommendation.

The severity of the condition is a central part of the need and solidarity principle. Assessment of the severity of the condition is affected by, for example, the risk of dying prematurely, the impact on

[1] QALY; quality adjusted life years
[2] ICER; incremental cost effect ratio

quality of life, impairment of physical functioning and, in the case of preventive treatments, possibly also consider the size of the risk of being affected by the disease in the future.

Consideration of the rarity of the disease can partly be attributed to the fundamental principle of human dignity and demands for equal treatment but also to the need and solidarity principle's writings about equal health outcomes. If the disease is very rare, there is a risk that treatments are not developed or provided unless society accepts a lower cost-effectiveness for these interventions.

The uncertainty in the clinical and health economic basis is also an important aspect to consider because it makes decisions less well-founded as uncertainty often means a risk of paying unreasonably for one treatment. In addition, considerations of uncertainty will incentivize the production of reliable data about new interventions. As a decision parameter, the uncertainty in the data is indirectly linked to the ethics of the platform, which requires that the benefit that is weighed in must "be based on science and documented good results" (Prop. 1996/97:60).

The NT and MTP councils' recommendations relate to commercial products where the companies that sell the products also set the price of the product. The price is the factor that the councils can potentially influence in a negotiation and has a direct impact on the cost-effectiveness of the intervention. This means that the assessment of the condition's degree of severity, rarity and the uncertainty of data need to be made in relation to the assessment of cost-effectiveness. Based on this balance, an assessment is done of whether the price the company offers can be accepted or whether a reduction is required for a positive recommendation in the form of “should” or “can”. The three criteria severity, rarity and uncertainty are graded into four levels: very high, high, moderate, and low. The criteria have different weights, and the severity of the condition has the highest weight of these. The cost effectiveness is expressed in SEK per quality-adjusted life year (SEK/QALY).

This is illustrated in the figure below.

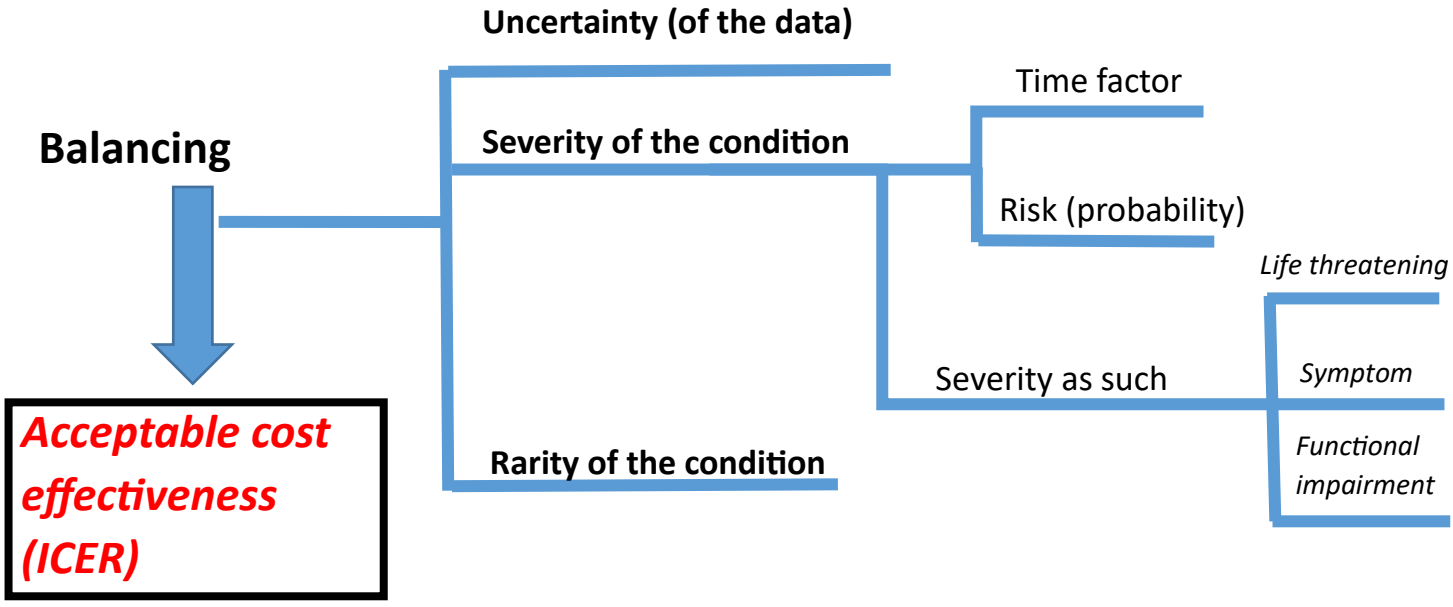

Figure 1. The relationship between the various factors that are weighed together to assess what is required in form of acceptable cost-effectiveness ratio. The acceptable cost-effectiveness ratio is set then in relation to the cost per QALY that the health economic analysis of the intervention showed. If it is higher than the cost per QALY, a positive recommendation for use can be given. In other cases, a price reduction is required for a positive recommendation.

Background

The main task of the NT and MTP councils is to make recommendations on the use of new interventions based on an overall assessment of the severity and rarity of the condition, the uncertainty in the clinical and health economic basis and the cost-effectiveness of the intervention. This assessment is based on an application of the ethical principles described in the parliament's ethical platform for priorities in healthcare (Prop. 60:1 9956/97). This policy applies to all interventions that the NT and MTP councils must decide on: medicines, medical technology and diagnostic products.

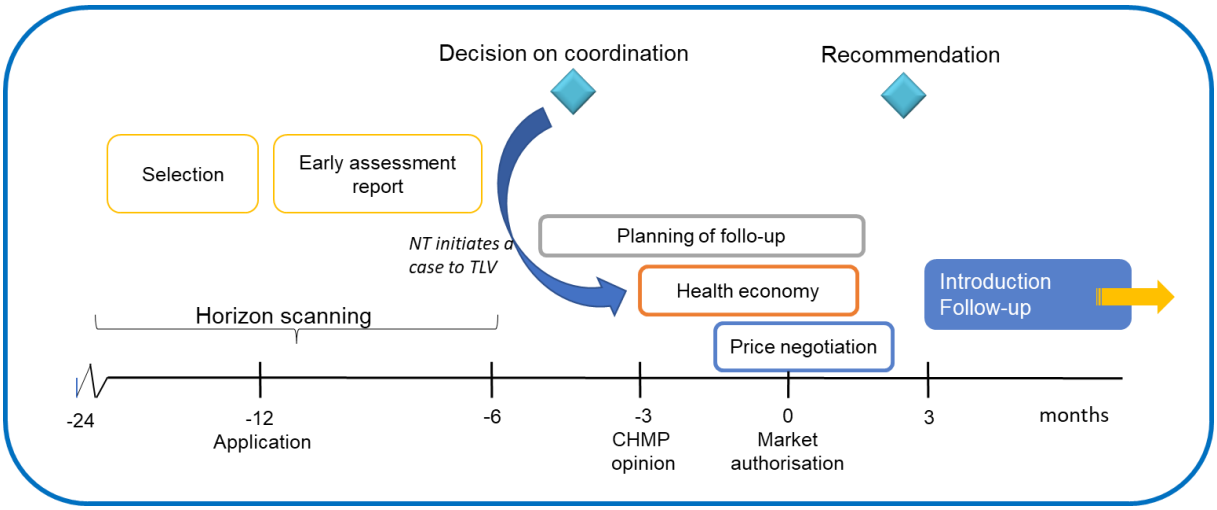

Figure 2. The NT Council's recommendation in relation to other activities within the framework of the regions' collaboration model for pharmaceuticals and the regulatory approval process.

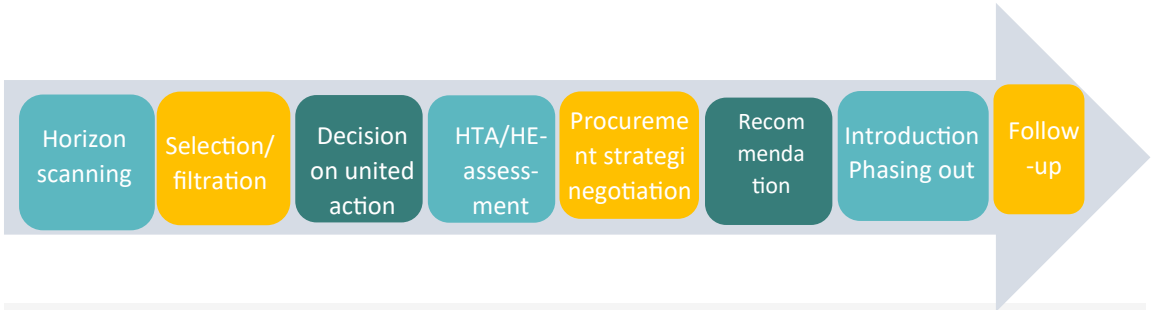

Figure 3. The MTP Council's process for producing a recommendation and follow-up. The biggest difference to the process for pharmaceuticals is that there is no regulatory approval process for medical devices and in vitro diagnostic products.

The Health Care Act and its writings about the ethical platform in chapter 3, §1 and chapter 4, §1 regulates the recommendations of the NT and MTP councils. The councils ' recommendations are also affected by The Act on Pharmaceutical Benefits because it is TLV (the Dental- and Pharmaceuticals Benefits Agency) that performs the health economic evaluations which are used in the councils ' recommendations and this law is the basis for how TLV interprets its mission regarding health economic evaluations. Value-based pricing is fundamental – i.e., that the price the tax-financed healthcare pays for an intervention should be in a reasonable relation to the benefit, given the

severity and rarity of the condition. This is expressed in §15, Act on Pharmaceutical Benefits, as that the price and subsidy must be decided so that the cost of using the medicine is reasonable, from medical, humanitarian, and societal perspectives. TLV's pharmaceutical benefits board (mainly prescription drugs), the NT Council (mainly requisition drugs) and the MTP Council (medical devices and diagnostic products) apply this by assessing how the interventions' cost-effectiveness relates to the conditions' severity, rarity and how great uncertainty that concerns the evaluation. This, in turn, is based on the principles adopted by the parliament; the ethical principles for priorities in healthcare (human values principle, need/solidarity principle and cost-effectiveness principle). The need-solidarity principle is superior and controls the application of the cost-effectiveness principle and thereby influences the degree of cost-effectiveness that should be accepted, while the human value principle forms an external framework for what may be weighed in the prioritization. According to the bill, the need/solidarity principle means that more of the health care resources should go to those who have the greatest needs, the most severe illnesses, and the worst quality of life in the purpose of equalizing differences in health. This applies even if not everyone gets their needs met. The size of the need depends on the severity of the disease (see below), but also assumes that the available treatment entails a relevant patient benefit. The ranking between the needs-solidarity principle and the cost-effectiveness principle means that society should pay more per meaningful health gain (patient benefit) for severe conditions compared to conditions of more moderate severity There are conditions that have such a low degree of severity that costs for an intervention should not be covered by society. However, the fact that the most seriously ill are prioritized does not mean that all resources can be allocated to them but the cost-effectiveness principle after all allows a reasonable relationship between costs and patient benefit also for less severe conditions. What weight difficulty is given in relation to cost-effectiveness is given limited guidance to in the platform. The advice is primarily based on that practice which was developed mainly in TLV's pharmaceutical benefits committee.

Fundamental in value-based pricing is establishing what a reasonable relationship is between the cost of the treatment and the amount of patient benefit the intervention provides expressed in quality-adjusted life years (QALYs) gained. The most important task of the NT and MTP councils is to assess for each intervention and indication (and possibly identifiable subgroups) if the relationship is reasonable and consequently whether the price of the intervention based on the health economic assessment is acceptable or needs to be adjusted, i.e. if an intervention is cost-effective in relation to the severity and rarity of the condition also taking into account uncertainties in the scientific and health economic data. It is important to distinguish between the health economic analysis and the ethical evaluation which is the basis for assessing what is a reasonable relationship between cost and benefit. In the health economic analysis different methods of calculation can give different costs per QALY (ICER = incremental cost effectiveness ratio), due to underlying assumptions about the effects of the intervention and other methodological considerations. The health economic analysis is based on certain value considerations being made, for example with regard to questions around how patient benefit should be assessed and whether production costs/gains and consumption costs respectively should be included in it the health economic model. Once these are made, however, no explicit ethical evaluation is made in it the health economic analysis, but this takes place when it is to be assessed whether the outcome of the analysis is reasonable given the above-mentioned considerations. Assessment of whether the calculated ICER is reasonable or not thus implies a broadening of the perspective and the actual decision on a recommendation presents difficult ethical trade-offs when new interventions are compared against already established ones. Determination of whether it is a reasonable relationship must therefore lean towards but also interpret the ethical platform which is laid down by the parliament. Determining what is an acceptable cost-effectiveness

ratio for a intervention and what is thus a reasonable relationship between cost and benefit can be done independent of the individual health economic evaluation and can therefore start before one has access to health economic data. This is based on an evaluation of previously made recommendations and there should be a rough idea of what is a reasonable relationship in advance. This is to ensure that decisions and recommendations are consistent over time. In many cases the health economic evaluation shows a cost that is clearly above or, someone times (more rarely), clearly below the level of what is a reasonable relationship why a rough estimate might be acceptable.

Another, and from a health economic perspective, more strict way of looking at what is a reasonable relationship, is that there is an absolute threshold that corresponds to the cost-effectiveness of the alternative use of the same resource for other urgent interventions in healthcare (or others for society important areas), i.e., the marginal productivity cost. This means that if the loss of health that occurs when not using the resource for other urgent interventions in ordinary healthcare is greater than the benefit one achieves from the use of the resource to pay for the new intervention, the threshold value for the willingness to pay has been exceeded. In scientific literature, the expression "health forgone" (opportunity cost) is used to represent the alternative health gain that the resource could have brought. The threshold value is thus determined by the value of the alternative use of the resource[3]. Attempts have been made to determine this threshold level empirically[4] , but it is a very complicated exercise that requires many assumptions, and this strategy has therefore been criticized. However, calculations of this threshold value suggest that it lies significantly below the levels that are usually considered to be the limit for cost-effectiveness in the Swedish the context. In a Swedish context, however, due to the need and solidarity principle, it is necessary to use different threshold values in different severe (and rare) conditions because this threshold value for reasonable cost-effectiveness is assumed to vary, as does the value one assigns to the opportunity cost. It means that we are prepared to accept a total loss of health (in individuals with a condition of average severity) for a smaller health gain by using a new intervention in individuals with conditions of high severity. Correspondingly, one is prepared to accept a total loss of health by forgoing the use of a new intervention for treatment of individuals with conditions of low severity despite being able to generate a greater health gain compared to the one previously accepted when treating individuals with a condition of average severity. Since this policy was first published in December 2015, even TLV in an indicative decision accepted a significantly higher threshold value for what is a reasonable cost-effectiveness of interventions with good efficacy in the treatment of rare conditions with high degree of severity.

A coherent model for priority recommendations for interventions in health care

One can imagine separating priority recommendations for different types of interventions and treat these separately, for example cancer drugs or drugs for the treatment of rare conditions as is the case in some other countries (England, France, Netherlands). In the pharmaceutical and pharmacy investigation (page 516 ff) suggestions were made that can be interpreted as to some extent manage drugs for rare conditions separately. However, these types of special handling are problematic since

[3] Anthony J Culyer. Cost-effectiveness thresholds in health care: a bookshelf guide to their meaning and use. Health Economics Policy and Law. 2016,:415-432. https://doi.org/10.1017/S1744133116000049

[4] Karl Claxton, Steve Martin, Marta Soares, Nigel Rice, Eldon Spackman, Sebastian Hinde, Nancy Devlin, Peter C Smith and Mark Sculpher Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold, Health Technology Assessment, Volume 19 issue 14 February 2015. http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0003/135480/FullReport-hta19140.pdf

they give rise to new problems in the form of new demands for special handling for other groups of patients in endearing situations or with a strong position in society. There is a risk that such solutions will make the work of achieving justice, equal care, and cost control more difficult in the pharmaceutical field. The pharmaceutical investigation SOU 2018:89 came to the same conclusion and judged that such special solutions would be a strong cost driver and cause a clear inequality between different patient groups. This policy is thus an attempt to, in a transparent and long-term sustainable way, preserve the value-based pricing and the common valuation of new interventions and describe uniform principles for this that apply to all types of interventions.

The ethical platform describes the principled foundation for what is an acceptable cost-effectiveness ratio and that it should vary in relation to needs. The model that is presented here can be seen as a slightly modified model compared to the one presented in the report "National model for open priorities in healthcare" Swedish National Centre for Priorities in Health 2017:2. The reason for this modification is that it deals with commercial products where the price is set by the companies. This means that initially there is a cost-effectiveness ratio (given various assumptions and method choices) for the product based on this price. The recommendations of the NT and MTP councils shall determine whether this cost-effectiveness ratio can be accepted given consideration of the other factors to be weighed according to the ethical platform. Another the difference is that the policy does not include the size of the patient benefit of the intervention as an individual explicit factor to consider. It (previously expressed as the effect size) has been included in the previous one version of the policy document. However, an in-depth analysis has shown that the effect size is included in the cost-effectiveness assessment and although it may have a role to play, this role is too complex (and co-varies with other factors) to be meaningfully weighed into the priorities that the NT and MTP councils make[5]. The patient benefit that the intervention entails will, however, still be described in the recommendation. Two aspects of patient benefit with potential relevance for recommendations are the cases when it represents a very modest (not relevant) patient benefit, respectively when it comes to a treatment that is apparently completely curative. However, since these require further delineation, we have chosen in this policy not to attribute these some additional weight in addition to what is already handled via the other factors:

a) the severity of the condition

b) the rarity of the condition

c) the uncertainty of the health economic basis (including the uncertainty in it clinical evidence)

Of these factors, severity can be directly attributed to the ethical platform's need- and solidarity principle, while consideration about rarity is based on an analysis of the ethical platform which concluded that the human value principle's idea of equal treatment, in combination with the need- and solidarity principle's ideal of equal health outcomes in the population provided support for lower cost-effectiveness levels could be accepted if necessary to ensure a more equal treatment opportunity for patient groups with rare conditions. Consideration of the uncertainty is supported by writings in the bill where the ethical platform is described that requires that interventions to be considered must "be based on science and documented good results" (Prop. 1996/97:60). Another reason why consideration of uncertainty is important is the opportunity cost and that great

[5] According to the national model, the patient benefit of the intervention must also be considered, this policy takes care of this by including the patient benefit in the cost-effectiveness ratio. National model is often used in contexts where there is no possibility to make cost-effectiveness considerations, which justifies its inclusion as one own factor.

uncertainty may lead to that resources are used on interventions that cannot justify the opportunity cost.

The severity of the condition

According to the need and solidarity principle, patients with the greatest needs should have access to more of healthcare resources than other patient groups. The needs of vulnerable groups need special attention and must be taken into account to the same extent as that of other groups so that the vulnerable groups do not receives worse than others. This means that one must define what is meant by need. According to the proposition, which is the basis of the ethical platform, need is linked to both the state severity, and the patient benefit of the intervention. Since the latter factor is weighed into the cost-effectiveness ratio, we focus here on the degree of severity. There are several aspects to consider in terms of severity:

1. Current condition:

How life-threatening is the condition now? How symptomatic? How much functional impairment or restriction of privacy/autonomy? How much is the overall quality of life influenced due to these aspects?

2. Future conditions:

a. The time factor. How long lasting is the condition? Will the condition worsen in the future?

b. The risk. How big is the individual's risk of acquiring a future illness (prevention or adjuvant[6] treatment)?

The impact of availability of standard treatment

Before we go into the different dimensions of severity, it is important to emphasize that the degree of severity must be assessed based on today's actual situation regarding the current condition, treated with available standard treatment. Some conditions would be assessed as very severe and acute life-threatening without available treatment, for example type I diabetes, HIV infection, or chronic myeloid leukaemia. Controlled with modern treatment, however, one can consider the conditions as less severe than without access to this treatment although of course still, in some cases they can cause significant inconvenience and some increased risk of late complications and premature death. Accordingly, patients who do not respond to the treatment available today are considered to have a condition of higher severity and may need to be handled as a sub-population.

Current state

Although mortality is in principle the ultimate negative event, other effects of the condition must also be considered, such as functional impairment and various symptoms. The current condition may need to be assessed separately in different phases of the same disease (stage, progression, etc.) and at different times during the course of the disease. According to the national model, the degree of severity is divided in four degrees; very high, high, medium, and low – a scale that the National Board of Health and Welfare also applies in its own national guidelines and TLV in their benefit decisions.

[6] Adjuvant treatment means a treatment given to prevent relapse in a cancer patient. In some cases, the patient will relapse despite the adjuvant treatment and in some cases the patient was already cured after initial treatment and did not benefit from the adjuvant treatment, but in some cases the adjuvant treatment may cure a patient who would otherwise have relapsed and died prematurely.

When considering mortality as part of the severity assessment, it can mainly be done in two different ways. By weighing how many years of life the patient (on a group level) will lose due to his condition, or by weighing in the time to death that the condition entails. In the first case, it would mean that a younger patient group who has a life-threatening condition is at risk of losing more years of life and thus have a higher degree of severity than an older patient group. The latest the Norwegian prioritization investigation and the subsequent Storting decision[7] was, for example, permeated by this principle. It thus means that a life-threatening disease in a group of young patients (with otherwise longer expected survival and thus greater loss) is considered more difficult than when a similar disease affects a group of elderly individuals. In the Swedish context, this has been interpreted that such an approach risks running afoul with the principle of human dignity's prohibition against factor in chronological age. The alternative is therefore to consider time to death instead, where shorter time to death means a greater degree of severity than if the patient group has a longer time to death. This basically means that in Swedish healthcare, a life-threatening illness is regarded as equally severe per se, regardless of which age group that is affected.

However, in the health economic analysis of the cost-effectiveness ratio, a curative treatment of a life-threatening disease will generate greater value in a younger patient group than in diseases which primarily affect patient groups at the end of life due to that cure earlier in life generates more QALYs compared to cure later in life. Even though this could also be interpreted as running afoul with the principle of human dignity, according to above, it appears to be less controversial and accepted by most, although not all, interpreters of the ethical platform. This also applies to the question of duration which dealt with in the next section.

Duration of the condition

According to the ethical platform, the degree of severity is also affected by the duration of the condition. It is difficult to find examples of serious, life-threatening conditions of short duration - if they are judged as serious despite their short duration, it is generally because they have a very large impact on quality of life during this time – or may lead to death within a short time. Generally, if a condition has a longer duration, it may be considered more severe than if it is transitory. Here we also need to consider whether the condition will deteriorate during its course.

Future state

For the individual who is affected, it is on the one hand irrelevant how great the risk of being affected once was, while on the other hand it is less serious to be part of a risk group at an earlier stage than to actually be affected by the disease.

This implies that treatment of manifest conditions will receive a systematically higher priority than prevention of the same condition. However, there are several reasons for prioritizing manifest conditions here and now in front of conditions that will with some probability occur within a more or less distant future.

The purely financial aspects of this are about expected economic development and what benefit an available resource today can generate in the future, however, is managed through discounting within the health economic model analysis.

Prevention means that more patients are exposed to the risk of side effects. If the time for prevention is long-term, there is also a risk of (at the start of treatment) unknown long-term side effects and that

[7] Verdier i pasientens helsetjeneste. Melding om prioritering. Meld. St. 34 (2015-2016), Innst. 57 S (2016-2017) https://www.stortinget.no/no/Saker-og-publikasjoner/Saker/Sak/?p=64494

infrequent, serious side effects may occur. The fewer patients that need to be treated to obtain a positive effect in one patient, the greater the value of the prevention.

Another aspect is that there may be new more effective interventions for treating the condition during the prevention period, which introduces an uncertainty about the future value of prevention used today. Such uncertainties always go in one direction, to worsen the cost-effectiveness of the prevention.

If there is an opportunity to defer treatment without there being a high risk of it affecting the course of the disease or the prognosis, also "patent expirations" or additional, competing therapies may mean that it is more optimal from a societal economic and priority point of view to delay treatment and prioritize patient groups with more immediate needs. For example, TLV and the NT Council initially prioritized the treatment of patients with hepatitis C stage 3 and 4, who has the most advanced fibrosis grades. Patients with a lower degree of fibrosis, of which a smaller fraction spontaneous heal and where in others it can take many years before progress, priority was lowered at an initial assessment by the NT Council. In light of rapidly falling drug prices due to competition, this turned out to be a wise strategy if you consider society's use of limited resources.

Regarding patient groups who currently have no manifest disease, but who have a risk of developing a disease state in the future, one thus needs to assess these separately. The probability of falling ill or relapsing should to some extent be weighed into the assessment of severity. The risk is both about the current degree of severity of the condition when it becomes manifest, and what is the probability of this happening. Generally, this means that the degree of severity of this form of risk condition consists of a consideration of the severity of the condition when it occurs, weighted against the probability that it will occur. If the probability is very high for future serious illness, the degree of severity should not be downgraded. For example, patients with acute myeloid leukaemia in remission at high risk of relapse. The other end of the risk spectrum include, for example, risk factors for future cardiovascular disease and death in the form of increased blood pressure and lipids as well as "lifestyle factors" in the form of being sedentary or being overweight. In this case it is practice to partially weight down the degree of severity even if these risk factors lead to severe conditions.

The rarity of the condition

The occurrence (prevalence) of a condition affects the possibility to finance the development of new medicines[8] . The cost of developing drugs against common diseases can be passed on to many users, and it is therefore unusual that medicines against popular diseases are priced so that the cost per QALYs is above the level that can be considered cost-effective. Despite this, the drugs are often very profitable for the companies. There are therefore good reasons why the willingness to pay should be kept relatively low when it comes to interventions for common conditions, especially if this can be linked to different forms of volume agreements between payers and drug companies.

Opinions that the willingness to pay for drugs against rare diseases should be higher are often expressed from both the profession, leading regional representatives and the general public in media. The issue has also been investigated and discussed in scientific literature[9]. In empirical research,

[8] In this section we talk exclusively about medicines because the consequences of rarity mainly affect medicines.

[9] Juth N1 . For the Sake of Justice: Should We Prioritize Rare Diseases? Health Care Anal. 2017 ;25(1):1-20. Lars Sandman, Erik Gustavsson The (Ir)relevance of Group Size in Health Care Priority Setting: A Reply to Juth. Health Care Anal. 2017 25(1):21-33

however, there is weak support for a general perception of a higher willingness to pay for medicines for rare conditions[10]. A reason to yet accept a higher willingness to pay is, as described above, that the cost of production of new medicines for very small patient groups is in principle (although rarely in practice) as high as for larger patient groups and that the development costs of drugs for rare conditions therefore risks being significantly higher per treated patient. However, the price set for medicines has probably very little to do with the development costs but more about an estimate of which price can provide maximum revenue. Regardless of this, the health and medical care needs to adapt to the fact that the development cost and profit must be calculated on a significantly smaller patient population. Likewise, decisions on the development of new drugs are to some extent governed by what price the market expects come to accept. In a partial investigation/appendix to the Medicines and Pharmacy investigation, the Swedish National Centre for Priorities in Health has analysed whether the ethical platform could provide support for an elevated cost-effectiveness threshold for medicines for rare conditions. It was concluded that an elevated threshold can be accepted under certain conditions. This is based on that the principle of human dignity stipulates that consideration of irrelevant factors must not affect the priorities, and the idea of equal treatment and equality which is expressed in the principle of human dignity and the principle of need and solidarity. Furthermore, that it is a very severe condition, that the intervention has a substantially greater patient benefit for the patient group (albeit not curative) than standard treatment and that it is a very rare condition (so-called ultra orphans) where the above economic arguments can be said to be applicable. It is important to emphasize that if the patient group is expanded when the intervention receives more indications, the latter reason may fall. This is emphasized if the indication for the intervention is extended to patient groups with conditions which also have a lower severity.

It Is thus rather the effect of the rarity of the conditions (the problem of financing the development costs in relation to income when they are to be distributed on a few treated individuals) than the rarity itself which justifies a higher cost-effectiveness threshold. Now there are after all today orphan drugs in the benefit system without having to raise the threshold for cost-effectiveness above what previously considered acceptable.

The model thus means accepting a higher cost-effectiveness threshold for treatment of rare conditions but only to a certain limit. This limit and the function (slope) of this new factor must still be determined based on which opportunity cost one is willing to accept for the current treatments. The principle can be illustrated with the figure below.

[10] Wiss J, Levin LA, Andersson D, Tinghög G. Prioritizing Rare Diseases: Psychological Effects Influencing Medical Decision Making. Med Decis Making. 2017 37(5):567-576

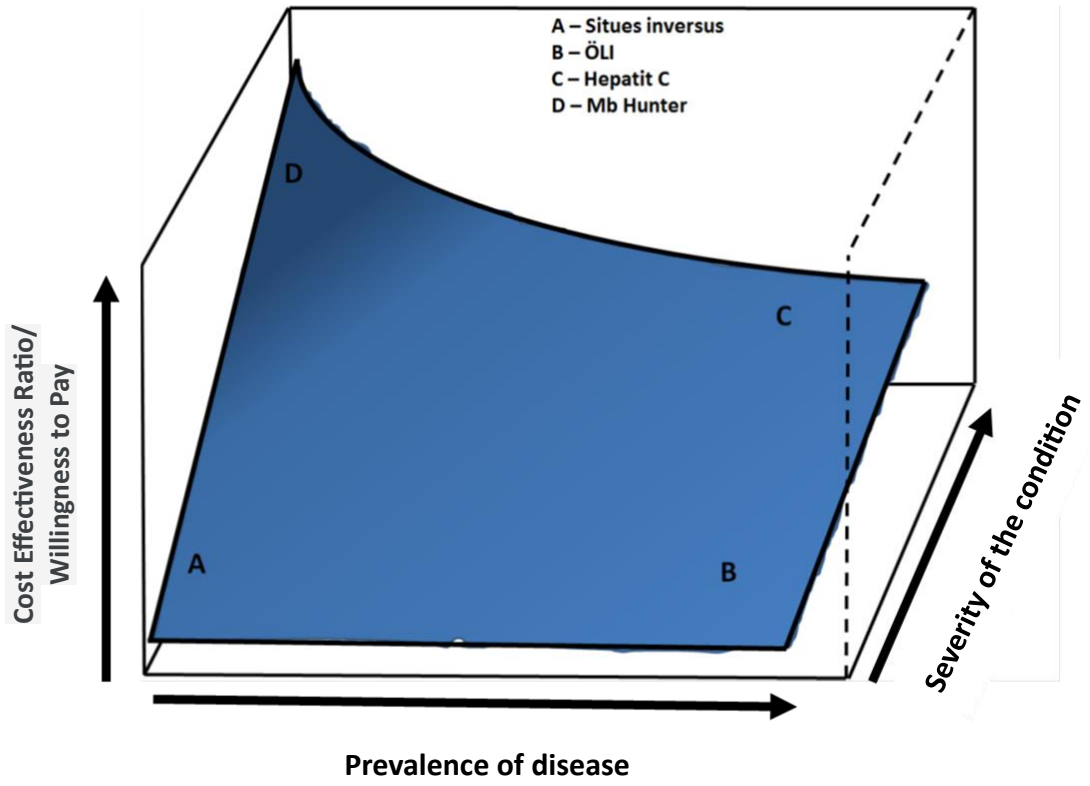

Figure 4. The relationship between disease prevalence, the severity of the condition and what is reasonable cost effectiveness ratio. The figure indicates that what is a reasonable price increases for treatment of rare conditions especially when the degree of severity of the condition is very high.

As can be seen from the figure, there is an upper limit to what is a reasonable cost-effectiveness ratio also for extremely rare diseases. For moderately rare diseases this ratio approaches that of common diseases. Rarity as the only factor for a worse cost-effectiveness ratio is thus normally not acceptable. This is illustrated in the figure of the straight base of the "surface". One can imagine a four-dimensional relationship where the uncertainty in the documentation also is handled. Unfortunately, this cannot be visualized in our three-dimensional universe, but may be described mathematically.

The uncertainty of clinical and health economic data

The uncertainty in and thus the quality of the data relating to the magnitude of the drug's effect on survival and quality of life can influence the assessment of whether an intervention should be recommended or not.

Clinical data

There is almost always uncertainty in the evaluation of the effect and safety of new interventions. There is a trade-off between the need for reliable data and early access to effective interventions. The high cost of clinical documentation that provides reliable data can also influence the incentives and the possibility of developing new interventions, especially for small patient groups. When the patient group is very small, the possibility to do is also limited in practice by the possibility to perform controlled studies and obtain reliable data.

The reliability of the clinical documentation is assessed on the basis of, among other things, study design and quality (risk of bias), study size (number of events, statistical power, precision), documentation relevance for the Swedish situation (comparison to standard treatment) and the

relevance of the outcome measures (patient-relevant outcome, e.g. quality of life or survival, in relation to surrogate variables or less relevant outcomes). Also results from mechanistic/preclinical studies that show a support for claimed mechanism of action as well as results from studies in earlier development phases are considered.

The health economic valuation

Regarding new interventions, study data are often more immature than for established interventions, which somewhat complicates the qualitative benefit/risk assessment, which is a dichotomous (yes/no) decision, and which is the basis for the marketing approval. However, the problem with immature data is even greater for the *quantification* of the benefit, which is central to the health economic analysis. Often it is not the clinical basis itself that is unreliable, but assumptions made in the models used in the health economic analysis. For example, the extrapolation over time of survival data (and data on freedom of progression) as well as indirect comparisons and network analyses which are sometimes required to analyse the relevant comparison standard treatment alternative as well as assumptions about drug consumption and wastage introduces often large uncertainties in the results. Extrapolations of non-significant survival trends across many years/decades is common and quality of life estimates are provided only exceptionally as original data from the pivotal studies but are based on assumptions based on data from studies in other populations.

From the point of view of the payer, there is an added value in that the benefit you pay for is reasonably reliable and similarly, uncertainty lowers the acceptable price for the intervention. Additional data during follow-ups over time, which increase the certainty of the health economic valuation, often also tend to show a smaller than expected benefit as preliminary data are often based on data from interim analyses. Mathematically, there is more to lose if a method turns out to have, for example, 3 times higher cost (per QALY) in reality, than was originally estimated in comparison with what you (as a payer) win if the cost is 3 times lower. In addition, the uncertainty in estimates of the ICER does not tend to be normally distributed but rather skewed towards the risk that the ICER is much higher than the estimate. To demand a reduced price for interventions whose effect estimates are uncertain introduces a risk that interventions that later prove to be cost-effective and valuable do not benefit patients and society until on a later stage. On the other hand, there is a risk of that interventions that later turns out not to "fill the bill" are introduced and displace more cost-effective interventions. Here there may also be reasons to consider the difficulty of stopping an on-going intervention or refrain from using interventions already introduced. To some extent the uncertainty problem can be handled with payment models that are based on so-called risk sharing or "pay for performance" between the payer and the drug company. However, it is not likely that the problem with uncertain bases will be able to be handled in such a way and moreover it has proved difficult to handle such agreements in practice due to inadequate follow-up systems. To reward production of reliable data will, in the long run, drive development towards a better basis, in the same way that today's regulatory requirements have improved data regarding efficacy and safety for drugs. It is important that TLV in its health economic documents is clear about the extent to which the uncertainty of the basal data is considered by making more conservative estimates (worst case scenarios) in cases where there is great uncertainty. Otherwise, there is a risk that the intervention will be "punished" double for the uncertainty (both within the health economic evaluation and in the ethical valuation). In summary, the data uncertainty should affect the accepted price to some extent.

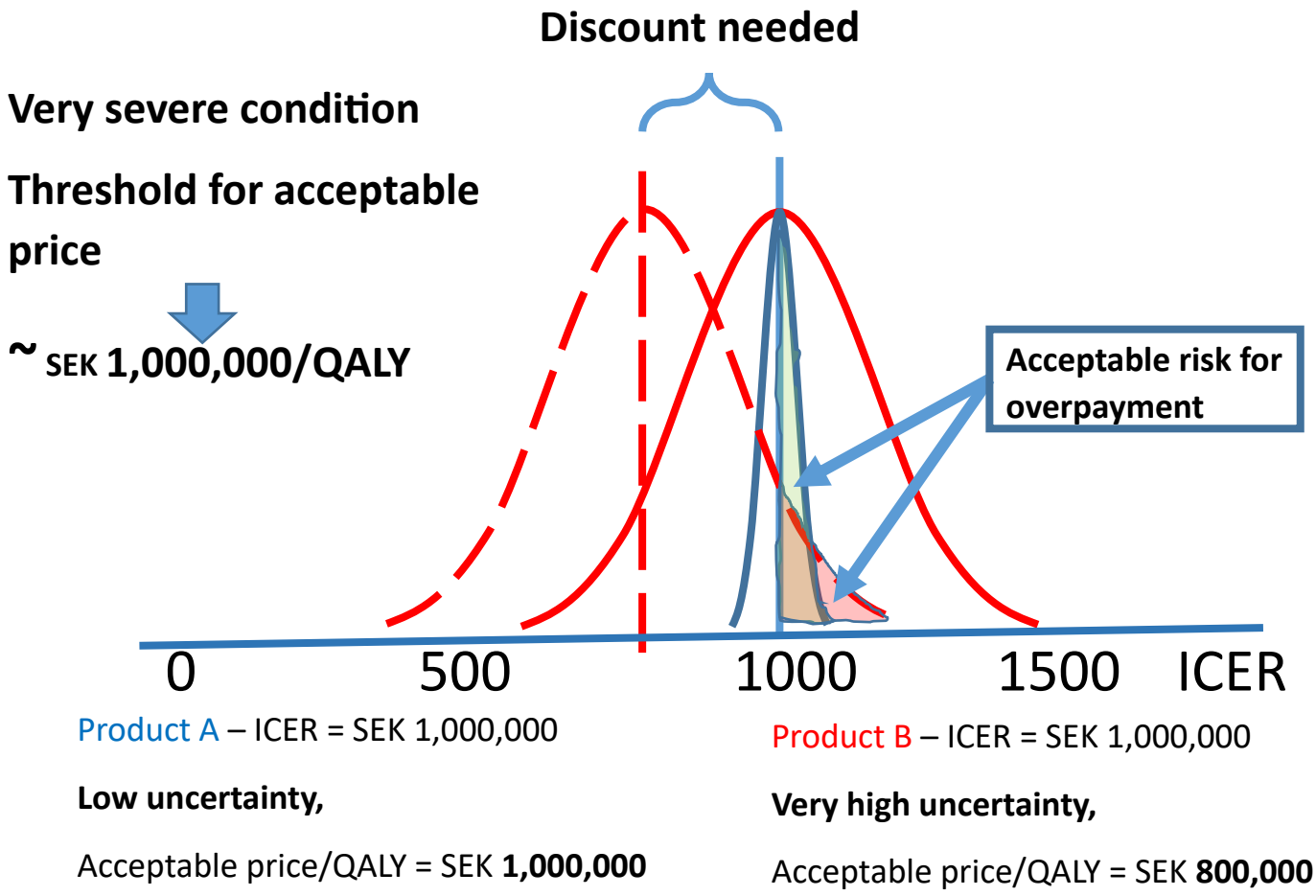

Figure 5. How uncertainty in the data affects the acceptable price of 2 otherwise equal interventions with different degree of uncertainty. The uncertainty has been illustrated here as normally distributed but is often skewed against very high ICER.

Underlying principles regarding the health economic assessment: Consumption and production costs

The question on how societal costs of consumption (including costs of continued treatment) in the case of life extension, respectively societal gains from increased productivity when patients can return to professional activities, has been discussed and analysed by TLV. There are different conceivable, opposing positions on these issues. Overall, however, it can be concluded that TLV has have become more restrictive in terms of including the so-called production value, i.e., the value of what a person is expected to produce if the intervention leads to improved work ability[11]. In their updated general advice for health economic evaluation, the recommendation is to make analyses both with and without indirect costs. The reason is that this otherwise risks discriminating against people who are not of working age and those who do not work for other reasons (e.g. severe

[11] TLVAR 2003:2 changed 2015:1

conditions). This approach is completely in line with the clear writings in the bill 1996/97:60. It is important that the NT and MTP councils and TLV's benefits board agree in their interpretation of the ethical platform in these respects. However, it can be worth considering the production value of the use of an intervention for treatment of a serious illness which preferentially affects individuals of working age if it is cost saving and bring great socio-economic gains which would otherwise not considered as cost effective.

Weighing of the factors for determining willingness to pay (the acceptable price)

The willingness-to-pay and value-based pricing models described here are primarily intended as support for the NT and MTP councils in developing recommendations based on TLVs health economic evaluations. The recommendations should clarify how the councils have considered the factors that influence the recommendation in each case. A transparent method guarantees consistency and predictability in decisions about recommendations and credibility towards the various consumers (regions/professions, patients, and affected companies). A couple of different ways of weighing the various factors together to arrive at reasonable decisions and recommendations over time can be considered.

Either you can:

a) build a mathematical model (according to traditional multi criteria decision analysis, MCDA) where different factors are assigned different values and weights, which gives a numerical value as a basis for decision or recommendation. The advantage is that considerations in various decisions become transparent and clear. The disadvantage is that it is difficult to fairly set the different values and weights that would be included in the model. It will necessarily be quite blunt and difficult to adapt to different conditions that may differ between different cases.

The other option is to

b) use a more qualitative approach where the various factors are described qualitatively. The advantage is that you avoid a way of working that is seemingly precise and instead adapts better to a reality that is complex. It also means that it is easier to manage other factors that may play a role in the individual case and that may be difficult to predict in detail. Here, however, there is a risk of ambiguity in the assessment and that recommendations may come to build on different assessments from time to time.

A third variant lays between the previous two by:

c) using a semi-quantitative working method that grades the various factors in 3-5 steps which can provide a clearer overview and facilitate assessment. The risk is, however, that an apparent objective image simplifies and distorts the perspective as different factors probably need to be weighted for a fair assessment.

One can also think of initially dealing with the issue in a semi-quantitative way and when more experience has developed, in a second step develop a quantitative decision model that in each case can form a support for the group's assessment. It may also be important to test and ensure that there is concordance in the assessments between different council members.

The following proposal for a semi-quantitative model as a basis for assessing the various factors needs to develop along with the practical implementation of the mindset described in this document. It would also be important to try to speed up the development of practice by going back and analyse previous decisions in the NLT group, the NT council and the MTP council to see how consistently one

already in the past in practice applied these principles and in which cases decisions or recommendations clearly deviate from the pattern. This is a comprehensive work but could very well be carried out within the framework of a research project or investigation by, for example, the Swedish Agency for Health and Care Services Analysis.

	Severity[12]	**Rarity (prevalence)**	**Uncertainty in the health economic evaluation**[13]
Grade 1	**Low** Troublesome but not agonizing No impact on survival	**Common condition** More than 200 patients in Sweden	**Very high**[14] An uncertainty that prevents all reasonable estimates of cost effectiveness
Grade 2	**Moderate** Handicapping, agonizing or some impact on survival	**Less common** Less than 200 patients in Sweden	**High**[15] Considerable uncertainty that clearly impairs the analyses of cost effectiveness
Grade 3	**High** Life shortening in a short or intermediate perspective or severely handicapping	**Rare condition** Less than 50 patients in Sweden	**Moderate**[16] Some uncertainty in the analyses of cost effectiveness

[12] Various factors such as the degree of life threat (mortality, loss of life expectancy), pain problems, disability and autonomy or loss of integrity (factors affecting quality of life) are weighted together into an aggregate assessment of the degree of difficulty. The assessment of severity applies to the current phase of the disease with available treatment or, the disease phase that the intervention intends to prevent. Some impact on survival means a median survival of more than 60 months. Short and intermediate perspective is between 12 and 60 months. Immediately life-threatening is a median survival shorter than 12 months.

[13] The uncertainty refers to the health economic basis, which also includes uncertainty regarding the clinical benefit be included. The uncertainty does not refer to the uncertainty in the decision situation itself, but the uncertainty in the basis which such. There are situations where the uncertainty with regard to whether the medicine has any at all effect is so monumental that the recommendation is to refrain from use regardless of price or condition degree of difficulty.

[14] Very high uncertainty, e.g., if clinical studies lack a control group or are based on outcomes that lacks clinical relevance or if the clinical data consists of only one or a few 10 or so patients, alternatively have major quality deficiencies. Very uncertain assumptions in the health economic model including highly uncertain extrapolations of efficacy data.

[15] High uncertainty, e.g., if the basis is based on a single, small but controlled clinical study with outcomes of questionable clinical relevance and/or where the follow-up time is so short that the patient benefit for the most part estimated by extrapolation of effect data in the health economic model. Non-randomized controls and indirect comparisons also involve a high level of uncertainty.

[16] Moderate uncertainty: for example, when is the outcome PFS instead of overall survival in a situation where this is justified or when the comparison alternative is acceptable even if not the one used in Sweden. Alternatively, when the evidence is based on a single RCT, although this is large. Alternatively, when estimation of the patient benefit is based to a significant extent on extrapolation of effect data.

Grade 4	**Very High** Immediate life-threatening or very agonizing condition	**Very rare condition**, Less than 10 patients in Sweden	**Low**[17] Low uncertainty in the assessment of cost effectiveness

Table X

Semi-quantitative estimation of factors of importance for willingness to pay.

Footnotes

1 QALY; quality adjusted life years

2 ICER; incremental cost effect ratio

3 . Anthony J Culyer. Cost-effectiveness thresholds in health care: a bookshelf guide to their meaning and use. Health Economics Policy and Law. 2016,:415-432. https://doi.org/10.1017/S1744133116000049

4 Karl Claxton, Steve Martin, Marta Soares, Nigel Rice, Eldon Spackman, Sebastian Hinde, Nancy Devlin, Peter C Smith and Mark Sculpher Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold, Health Technology Assessment, Volume 19 issue 14 February, 2015. http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0003/135480/FullReport-hta19140.pdf

5 According to the national model, the patient benefit of the intervention must also be considered, this policy takes care of this by including the patient benefit in the cost-effectiveness ratio. National model is often used in contexts there there is no possibility to make cost-effectiveness considerations, which justifies its inclusion as one own factor.

6 Adjuvant treatment means a treatment given to prevent relapse in a cancer patient. In some cases the patient relapses despite adjuvant treatment and in other cases the patient was already cured after the initial treatment and did not benefit from the adjuvant treatment, but in some cases the adjuvant treatment may entail that a patient is cured who would otherwise have regained their disease and thereby risked premature death.

7 Verdier i pasientens helsetjeneste. Melding om prioritering. Meld. St. 34 (2015-2016), Innst. 57 S (2016-2017) https://www.stortinget.no/no/Saker-og-publikasjoner/Saker/Sak/?p=64494

8 Utgår

9 In this section we talk exclusively about medicines, because the consequences of rarity mainly work affect medicines.

[17] Low uncertainty: the scientific basis is based on studies with appropriate design, good quality and good transferability to the intended patient group. The follow-up is so long that the estimate of patient benefit is mainly based on observed data and only to a lesser extent on extrapolations or that such extrapolations are based on reliable historical data.

10 Juth N1 . For the Sake of Justice: Should We Prioritize Rare Diseases? Health Care Anal. 2017 ;25(1):1-20. Lars Sandman, Erik Gustavsson The (Ir)relevance of Group Size in Health Care Priority Setting: A Reply to Juth. Health Care Anal. 2017 25(1):21-33

11 Wiss J, Levin LA, Andersson D, Tinghög G. Prioritizing Rare Diseases: Psychological Effects Influencing Medical Decision Making. Med Decis Making. 2017 37(5):567-576

12 TLVAR 2003:2 ändrad 2015:1

13 Various factors such as the degree of life threat (mortality, loss of life expectancy), pain problems, disability and autonomy or loss of integrity (factors affecting quality of life) are weighted together into an aggregate assessment of the degree of difficulty. The assessment of severity applies to the current disease phase with available treatment alternatively, the disease phase that the intervention intends to prevent.

16 The uncertainty refers to the health economic basis, which also includes uncertainty regarding the clinical benefit be included. The uncertainty does not refer to the uncertainty in the decision situation itself, but the uncertainty in the basis which such. There are situations where the uncertainty with regard to whether the medicine has any at all effect is so monumental that the recommendation is to refrain from use regardless of price or condition degree of difficulty.

17 Very high uncertainty is e.g. if clinical studies lack a control group or are based on outcomes that lacks clinical relevance or if the clinical data consists of only one or a few 10 or so patients, alternatively have major quality deficiencies. Very uncertain assumptions in the health economic model including highly uncertain extrapolations of efficacy data.

18 High uncertainty is e.g. if the basis is based on a single, small but controlled clinical study with outcomes of questionable clinical relevance and/or where the follow-up time is so short that the patient benefit for the most part estimated by extrapolation of effect data in the health economic model. Non-randomized controls and indirect comparisons also involve a high level of uncertainty.

19 Moderate uncertainty: for example, when is the outcome PFS instead of overall survival in a situation where this is justified or when the comparison alternative is acceptable even if not the one used in Sweden. Alternatively when the evidence is based on a single RCT, although this is large. Alternatively, when estimation of the patient benefit is based to a significant extent on extrapolation of effect data.

20 Low uncertainty: the scientific basis is based on studies with appropriate design, good quality and good transferability to the intended patient group. The follow-up is so long that the estimate of patient benefit mainly based on measurement data and only to a lesser extent on extrapolations or that these are based on reliable historical data.

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[13]Olika faktorer som graden av livshot (dödlighet, förlust av livslängd), smärtproblem, handikapp och autonomi eller integritetsförlust (faktorer som påverkar livskvalitet) vägs ihop till en sammanlagd värdering av svårighetsgraden. Bedömningen av svårighetsgrad gäller den aktuella sjukdomsfasen med tillgänglig behandling alternativt den sjukdomsfas som interventionen avser att förebygga.

[16]Osäkerheten avser det hälsoekonomiska underlaget i vilket även osäkerhet avseende den kliniska nyttan inkluderas. Osäkerheten avser inte osäkerheten i själva beslutssituationen utan osäkerheten i underlaget som sådant. Det finns situationer då osäkerheten med avseende på om läkemedlet över huvud taget har någon effekt är så monumental att rekommendationen blir att avstå från användning oavsett pris eller tillståndets svårighetsgrad.

[17] Mycket hög osäkerhet är t.ex. om kliniska studier saknar kontrollgrupp alternativt baseras på utfall som saknar klinisk relevans eller om det kliniska underlaget består av endast något eller några 10-tal patienter,

alternativt har stora kvalitetsbrister. Mycket osäkra antaganden i den hälsoekonomiska modellen inklusive mycket osäkra extrapoleringar av effektdata.

[18] Hög osäkerhet är t.ex. om underlaget baseras på en enstaka, liten men kontrollerad klinisk studie med utfall av tveksam klinisk relevans och/eller där uppföljningstiden är så kort att patientnyttan till största delen uppskattats genom extrapolering av effektdata i den hälsoekonomiska modellen. Icke-randomiserade kontroller och indirekta jämförelser innebär också en hög osäkerhet.

[19] Måttlig osäkerhet: exempelvis när är utfallet är PFS istället för totalöverlevnad i en situation där detta är motiverat eller när jämförelsealternativet är acceptabelt om än inte det som används i Sverige. Alternativt när underlaget baseras på en enda RCT, även om denna är stor. Alternativt då estimering av patientnyttan baseras till en betydande del på extrapolering av effektdata.

[20] Låg osäkerhet: det vetenskapliga underlaget baseras på studier med lämplig design, god kvalitet och god överförbarhet till den avsedda patientgruppen. Uppföljningen är så lång att estimatet av patientnyttan huvudsakligen baseras på mätdata och endast till en mindre del på extrapoleringar eller att dessa baseras på tillförlitliga historiska data.

Bilaga 1 - Introduktion till hälsoekonomisk utvärdering

Se: https://www.tlv.se/download/18.467926b615d084471ac3396b/1510316350460/introduktion-halsoekonomi.pdf