



Zorginstituut Nederland

Cost-effectiveness in practice

Date 26 June 2015
Status Definitive

Colophon

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Issued to	Minister of Health, Welfare and Sport

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Summary

All of us pay a premium for basic health insurance. Ours is an efficient system based on mutual solidarity: between young and old, the healthy and the sick, rich and poor. This solidarity has to be safeguarded. We can do this by showing that premium funds are spent optimally.

There are boundaries to the health care budget. Within those boundaries choices have to be made in order to arrive at an optimal division, to be sure society as a whole gets the best possible health gains. Cost-effectiveness is a criterion that helps us make those choices. It sets costs off against the effects of a form of treatment and thus gives us insight into which option gives the best 'value for money'. This is no different to what takes place in all sorts of fields outside health care, and in our own everyday decisions.

Using cost-effectiveness as a basis for decisions in health care is controversial. A much-heard argument is that it would not be ethical to allow costs to play a role in such choices. The Zorginstituut feels, however, that it would be unethical to avoid discussing this topic. After all, in view of our limited budget, if we do not ask 'how valuable is it to us?', choices may be made that result in a net health loss for society as a whole. In that case cost-effective care would be replaced by care that is less cost-effective. The impact of these choices is less visible though, because they are made arbitrarily and without transparency.

Arguments may exist for not always choosing for the maximum health gain per euro. This is why cost-effectiveness will never be the only criterion on which our advice is based. All our advice involves an integral weighing up of the package criteria efficacy, cost-effectiveness, necessity and feasibility, as well as other relevant arguments. Furthermore, we are also aware of the methodological vulnerabilities of cost-effectiveness. This is why we always involve the facts behind the statistics and we take uncertainties into account in our deliberations. However, this does not diminish the principle that cost-effectiveness must be an important criterion in our weighing up. It forms an important basis for our package advice when used in this balanced way.

Cost-effectiveness also plays a role in package decisions in other countries, particularly those made by NICE in the UK, where for decades they have employed a cut-off point at which an intervention is not reimbursed. Nowadays NICE also takes a more balanced approach, certainly when assessing treatments used in end of life situations. Countries such as France and Germany pay less attention to costs per QALY (Quality-Adjusted Life-Years), and more to the size of the effect of treatment. As people are prepared to pay more for a bigger effect, this correlates closely with our proposed approach.

When calculating the cost-effectiveness of a new treatment, the costs and effects are set off against the costs and effects of the existing treatment. The relationship between these costs and effects is the incremental cost-effectiveness ratio (ICER). Costs are expressed in Euros, and effects in QALYs. This is a standardised measure: one QALY stands for a year spent in good health. QALYs make it possible to compare the cost-effectiveness of different forms of treatment with one another. Four combinations are possible:

- the new treatment is better and more expensive than the old one;

- the new treatment is worse and more expensive than the old one;
- the new treatment is better and cheaper than the old one;
- the new treatment is worse and cheaper than the old one.

In the last three cases, practice generally follows suit. All sorts of agreements are made about good care at an acceptable price between the three parties: patients, care providers and care insurers. However, in the first case it is difficult for these parties to arrive at agreements. After all, who determines how much health gains are allowed to cost? This demands societal frameworks. These are issues for the package manager: the Zorginstituut. This is the main topic of this report.

In order to determine a framework, we first need reference values. This report proposes reference values that vary based on the burden of disease calculated according to the proportional shortfall method. Research into existing solidarity in health care shows that our society feels higher costs per QALY are justifiable when serious diseases are involved. Since the RVZ report, *Justifiable and sustainable care* (2006), the societal debate makes use of a cost ranging from 10,000 euro/QALY with a low proportional shortfall, to 80,000 euro per QALY with a high proportional shortfall. For the moment, the Zorginstituut has adopted this range as basis. It can of course always be adjusted based on (inter)national research.

As point estimates are involved both for cost-effectiveness and for proportional shortfall, we prefer to classify into three classes instead of using a sliding scale.

Burden of disease	Maximum additional costs (€) per QALY
From 0.1 up to and including 0.4	Up to €20,000 per QALY
Between 0.41 and 0.7	Up to €50,000 per QALY
Between 0.71 and 1.0	Up to €80,000 per QALY

Most care included in the basic package, including all care provided by medical specialists, has been given an open description. This means that new care is included in the package as soon as the parties in health care have agreed that care fulfils the statutory, generically determined requirements. The most important statutory requirement is that of proven effectiveness, or compliance with 'established medical science and medical practice'. Where there is a lack of clarity, the Zorginstituut can issue an 'outcome of assessment' [*standpunt*], e.g. if there is a risk of ineffective care being reimbursed, or effective care not being reimbursed, or if other risks arise relating to the collectively insured package.

Based on the reference value for cost-effectiveness that the Zorginstituut proposes in this report, the parties can signal whether new care has been included within the open system of insured care that may have an unfavourable or especially uncertain ICER and therefore requires an assessment by the Zorginstituut. In addition, the Zorginstituut will continue to initiate such assessments itself. Where possible we will enrich our outcome of assessments with statements about cost-effectiveness.

Advice on the contents of the basic package will always be determined in discussion with the parties. Treatment guidelines with recommendations based on cost-

effectiveness data could play an important role here. We have noticed that cost-effectiveness is increasingly a topic in treatment guidelines, though the lack of cost-effectiveness research data is still an important bottleneck. More expertise is needed among guideline developers as well as financial support for processing cost-effectiveness considerations in guidelines.

The method of package management is still under development. Elaborating the cost-effectiveness criterion, however, brings us one step further. It also gives rise to new questions, however, e.g., about the relationship between weighing up the cost-effectiveness criterion and weighing up other arguments, and about the course of this weighing up process. These questions will be addressed during the next six months, when we elaborate upon the Weighing up Framework for package management with the parties. An important point for attention will be elaborating on the proportional shortfall approach of calculating the burden of disease. During the next few months we will examine whether this approach is in sufficient alignment with current societal opinions.

The consideration of cost-effectiveness will become increasingly important when issuing advice on the collectively insured package. We feel that its anchoring in laws and legislation, as included in the Coalition Agreement, is extremely desirable, not as a knock out-criterion, but as a criterion alongside effectiveness, necessity and feasibility, whereby these criteria are jointly weighed up.

1 Introduction

1.1 What is cost-effectiveness?

The cost-effectiveness criterion enables us to make choices in health care. It clarifies the relationship between the efficacy of treatment (how does treatment benefit a patient?) and the costs that must be incurred to achieve this effect. It involves comparing a new treatment for a disorder with the "old" one. Research must establish that on average the treatment is effective for the group of patients for which it is intended.

In effect, cost-effectiveness is not just about costs, but rather about the effects of an intervention. If they are minor, then the cost-effectiveness is more likely to be unfavourable. Effects and all cost-consequences (i.e., not just the price) of a (new) treatment will be set off against the treatment normally used up till that moment. Effects are expressed in life-years gained, with corrections for quality (QALY or quality-adjusted life-year). Cost-effectiveness is expressed in costs per QALY. Such a standardised measure makes it possible to make comparisons with interventions for other disorders.

The terms cost-effectiveness and efficiency are often used interchangeably. Efficiency is a broader concept than cost-effectiveness. It can be sub-divided into:

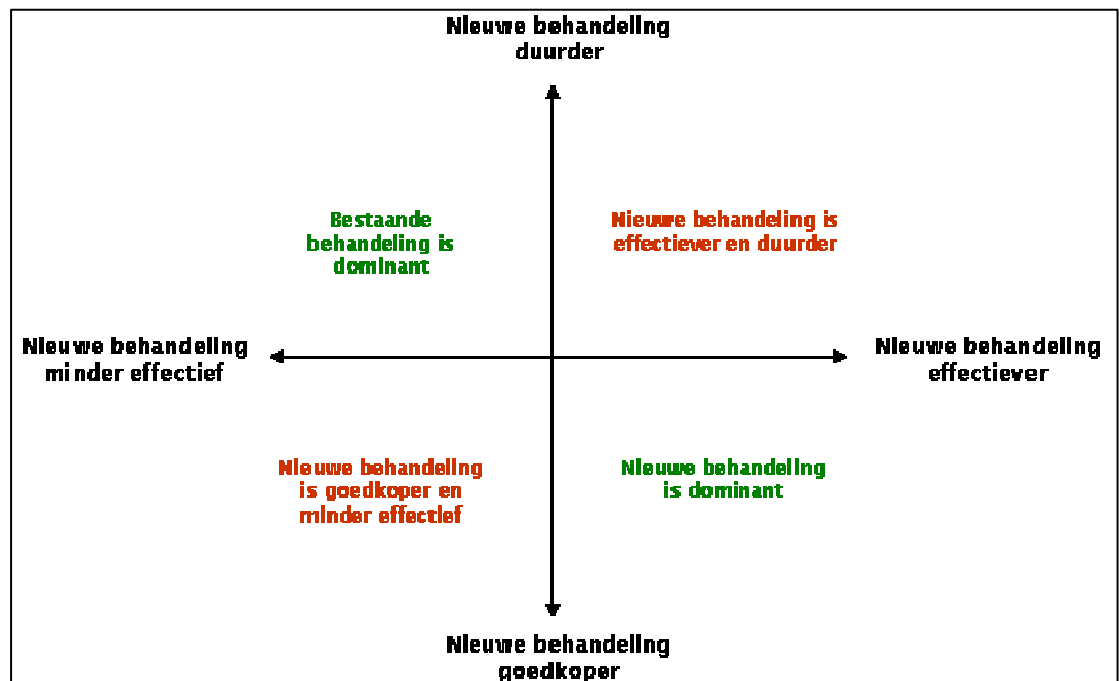
- technical efficiency: ensuring no resources are wasted;
- cost-effectiveness: choosing the product with the lowest possible costs;
- allocative efficiency: choosing the most cost-effective option.

The second and third situations are also referred to as cost-effectiveness.

There are four possible outcomes when we compare the effects and costs of a new and a usual treatment with one another (see figure):

- the new treatment results in health gains at lower costs;
- the new treatment results in health losses at lower costs;
- the new treatment results in health losses at higher costs;
- the new treatment results in health gains at higher costs.

In the first three cases, practice generally follows suit. All sorts of agreements are made about good care at an acceptable price between the three parties: patients, care providers and care insurers. However, in the last case it can be difficult for these parties to arrive at agreements. After all, who determines how much health gains are allowed to cost? This demands societal frameworks. These issues can be placed in the lap of the package manager: the Zorginstituut. They mainly relate to new care that results in health gains at higher costs. Or where this is at least strongly suspected, because in fact, often no convincing evidence of effectiveness (or cost-effectiveness) has yet been supplied for a new treatment. How is this choice made?



1.2

Justifiable choice

Regular discussions have taken place in the Netherlands in recent years about the role that cost-effectiveness should play in reimbursement decisions. Cost-effectiveness has always been one of the package criteria used by the Zorginstituut because we feel it is a justifiable criterion. Clearly, different opinions exist about what is justifiable. For instance, some people feel that resources should be deployed in order to reduce the differences between people's state of health as far as possible. Other people feel that resources should be divided in such a way that the greatest possible health gains are achieved for the entire population. These opinions exist alongside one another within every society. Depending on the circumstances, sometimes it may be preferable to help a smaller group of people with a poor state of health, and at other times to promote the state of health of a much broader group. What is particularly important is that the process in which the choices are made is transparent. This is known as procedural justice.¹ The Zorginstituut is doing all it can to design a process that is just, transparent and meticulous.

What if cost-effectiveness played no role?

Everyone remembers the commotion that arose after the publication of the report by the Zorginstituut (then still CVZ) about medicines used to treat the diseases of Pompe and Fabry. Many parties disputed that cost-effectiveness should be allowed to play a role in package decisions. But what happens when you do not allow it to play a role?

If the demand for care had to be funded entirely from collective resources, the costs would be much greater than the financial resources provided by society. This means that choices have to be made. In order to make these choices, we want to know which health gains result from the deployment of certain interventions. If we do not, society may end up spending money on interventions that result in relatively few

¹ Daniels N, Sabin JE. *Setting limits fairly: Can we learn to share medical resources?* Oxford: Oxford University Press, 2002: It provides explicit accountability for the choices made. Daniels and Sabin show, using their A4R (accountability for reasonableness) framework, the importance of such an explicit framework

health gains for patients.

An example: according to the "costs of diseases study" carried out by the RIVM, the costs of mental disorders amounted to 15,895 million euro in 2011. This was 21.4% of the total available budget and thus the largest "cost item". In second place came the costs of cardiovascular disorders, with 6,911 million euro (9.3% of the total budget). We feel it is important to know what health gains have resulted from the money we spent on these diseases. Or in concrete terms: to what degree does a patient with an anxiety disorder benefit from cognitive behavioural therapy or does a patient with severe depression benefit from being admitted to a GGZ institution? And how much do patients with constricted blood vessels benefit from having a stent placed? And how much money do we have to invest in order to capitalise on these health gains or do other more profitable alternatives exist? We make use of the cost-effectiveness criterion in order to reply to these questions.

To do this, we need to know the size of the available budget. However, there is no single moment at which a decision is made to include interventions in the package. Interventions simply get included in the "open system" as soon as they fulfil the statutory criteria. Insofar as a "limiting description" exists, then a specific decision is required from the Minister, but this takes place throughout the year². As a result, at the moment of making a choice, no clarity exists about which benefits of alternative spending options (the opportunity costs) will be lost and which patients will not receive reimbursement because they opted for a given treatment (the displacement effect).

Research recently took place in the UK into the consequences of applying NICE's current upper limit for cost-effectiveness³. This currently assumes an upper limit of 20,000 to 30,000 pounds (between 28,000 and 42,000 euro). The research shows that this upper limit may be too high because it is resulting in net loss of health gains for the population. This is mainly because other patients are not receiving reimbursement for their treatment or are having to wait longer for it. These are often patients who receive less attention from the media and who are less able to demand attention for their disorder. Naturally, the UK's system is quite different from ours in the Netherlands, so that the results of this research cannot simply be transposed onto the Dutch situation. But it does encourage us to think about the consequences of positive advice. Perhaps similar research can be carried out in the Netherlands so we can get a better idea of the displacement effect.

In the Netherlands it has been agreed that the yearly growth in health care costs has to be very limited (1% for 2015). If no explicit choice is made on a national level as to where this growth is allowed, then the choice is made implicitly (i.e., invisibly) in implementation. In other fields than public health, explicit considerations are made between the costs and benefits of measures. Examples of this are roads, raising or fortifying dikes and making workplaces safer. In these fields concepts such as 'value of a statistical life' (VSL) and 'value of a statistical life-year' (VSLY) are common practice. Wherever the available amount of money is limited, choices will have to be made between risk-limitation and costs. Such choices are ethically defensible if we consider it important to prevent as many accidents and deaths as possible with a limited amount of money⁴. The same applies when choices are made in health care. One could even say that failing to make

² The package has been given a largely open description in order to keep it flexible. As a result no explicit decision-making is necessary. Where it is necessary the Zorginstituut can issue (risk-oriented) outcome of assessments in which care is examined in light of statutory criteria. Part of the system is closed (extramural medicines); the Minister makes an explicit decision on these after receiving advice from the Zorginstituut

³ *Karl Claxton ea.* Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold, *February 2015*

⁴ Taken from: Article Job Kievit "what's it worth to us?",

explicit choices is ethically indefensible. After all, this means there is no transparency/visibility for which groups of patients consequences of choices exist (e.g., displacement effects) and whether those consequences are acceptable.

1.3 Cost-effectiveness in historic perspective

Examining cost-effectiveness in health care has been high on the government's agenda for decades. A milestone was the advice 'Inescapable choices' of the Dunning Committee in 1991, in which the famous 'Dunning funnel' saw the light of day: making choices in health care based on the criteria necessity, effectiveness, cost-effectiveness, and at one's own expense and accountability. The committee proposed, among other things, that limits could be imposed on (reimbursing) care where costs were high and benefits limited, and indicated that they envisaged an important role for professionals in realising this. The guiding principle for medical interventions would not be limited to the interest of an individual patient, but would include the interest of society.

Nevertheless, it has taken years for the discussion about using cost-effectiveness in health care to really get off the ground. Possibly because there was no real need to allow the criterion to play a role in choices in health care. Now that budgetary frameworks inside and outside health care have become relatively tighter, considering the matter of allocation has become more urgent than ever.

1.4 The Minister's questions

The Minister asked CVZ (the legal predecessor of the Zorginstituut) (letter to the lower house regarding strict package management dated 15 June 2012 and letter on points for attention dated 18 July 2012) to elaborate upon the cost-effectiveness criterion. An additional question in relation to this was to examine whether use could be made (and if so, to what extent) of the way in which NICE uses the cost-effectiveness criterion in the UK in decisions about accepting interventions for inclusion in the insured package. This was in response to the adopted Voortman resolution (Lower House 2011-2012, 29 689, no. 400). On 29 October 2012, the VVD-PvdA coalition agreement was formed after the points of attention letter had been sent. The coalition agreement called for "selectively but systematically mapping out cost-effectiveness" within the context of "stricter package management". The government was of the opinion that this demanded statutory anchoring of the criterion. This resulted in the Minister issuing the Zorginstituut with an additional task on 20 December 2012 of elaborating upon the various options for statutory anchoring. This meant that the Zorginstituut had to deal with three requests:

- elaborate upon the cost-effectiveness criterion;
- examine the way in which NICE works and what the Netherlands could learn from this;
- propose possible scenarios for a statutory anchoring of the cost-effectiveness criterion.

These requests show that the Minister wanted cost-effectiveness to play a more emphatic role in package management. The letters are enclosed with this report as Appendix 1.

This report describes how we envisage deploying the cost-effectiveness criterion within this modern form of package management. We define modern package management as package management that is not limited to only the classic "yes and no" decisions about reimbursement, but where the parties search together for situations in which the use of an intervention is both effective and cost-effective.

The Minister speaks of "strict package management". The Zorginstituut prefers to call it "appropriate care".

Such policy shifts responsibility more onto the shoulders of the parties; they are responsible for making sure the package is used optimally. The downside is that package management and its use may become intertwined. After all, the process seems to be decreasingly linear, with a decision first being taken and the parties then starting to use care.

This report also draws attention to this matter.

This publication is one of a series about methods of package management, including various editions of the report "Package management in practice" and the report "Assessment of established medical science and medical practice" (a new version of which was recently published). These publications are intended to provide a picture of developments in the evaluation framework of package management.

1.5 Accountability for the approach taken and the involvement of health care parties

In the summer of 2012, when there was a lot of commotion surrounding the publication of draft advice on medicines for the diseases of Pompe and Fabry, the Zorginstituut felt that the time had come to elaborate on this sensitive topic. We therefore organised a number of activities relating to the topic of cost-effectiveness in recent years, namely:

- Kitchen-table discussions with care providers, patients and citizens in various locations in the country.
- A so-called package debate about cost-effectiveness and care in end of life situations.
- An initial report announcing that the Zorginstituut would elaborate on the topic via various tacks.
- The cost-effectiveness programme, comprised of the topics: updating the guidelines for health-economic research, cost-effectiveness and purchasing care, cost-effectiveness and guidelines, cost-effectiveness and its statutory anchoring and cost-effectiveness and integral considerations.

Within the framework of the different "research tacks" in the cost-effectiveness programme, we organised regular sessions with health care parties in various formations in order to exchange ideas interactively. This report is a compilation of the results of the programme. The report was also sent to all parties for administrative consultation. The following organisations responded to the draft report:

- NVZ
- KNOV
- The Federation of Medical Specialists
- the Association of Dutch Health Insurers
- Public Health and Society Council
- NFU
- Verenso (no substantive response)
- GGZ Nederland
- Holland BIO and Nefarma
- NHG
- Collaborating patients' organisations
- Netherlands Paramedical Platform (PPN)

- NEFEMED
- KNMP (Royal Dutch Association for the Advancement of Pharmacy)
- KNGF (Royal Dutch Society for Physical Therapy)

Insofar as possible, the Zorginstituut has incorporated responses received from these parties in the text. We sent individual letters to each organisation in response to all the points they brought up. On 2 October 2014 a consultation meeting was held with the parties on the topic of using reference values and on 22 April 2015 a meeting was held with the parties within the framework of the administrative consultation on the draft report. The reports on both meetings are enclosed with this report as appendices 2 and 3 respectively.

The draft report was discussed on a number of occasions with the Insured Package Advisory Committee. The committee's comments have been fully incorporated into the report.

1.6

Structure of this report

The following section describes the form that the Zorginstituut wants to allow the cost-effectiveness criterion to take. After this, in section 3, we discuss the consideration of cost-effectiveness relative to other arguments in society-based evaluation. This includes a description of the statutory context as well as a demonstration of the proposed working method by making use of examples. We also use these examples to show what the parties themselves can contribute to realising cost-effective care. In section 4 we discuss the important role that treatment guidelines can play when recommendations are based on cost-effectiveness considerations. Lastly we have drawn up a list of a number of important conclusions and we return to the Minister's questions (section 5).

2 Cost-effectiveness and package management: elaboration of the assessment

2.1 Introduction

The Zorginstituut has been instructed to safeguard the accessibility, affordability and quality of the insured package. In fulfilling this task, they are advised by expert committees, namely the Scientific Advisory Board (WAR) which advises on scientific assessment of effectiveness and cost-effectiveness, and the Insured Package Advisory Committee (ACP) which advises on societal implications of package advice.

Because the basic insurance is largely an open system, the parties themselves play an important role in determining what care is used and reimbursed. The outcomes of assessment and advice issued by the Zorginstituut are mainly about marginal "grey areas" of the package where questions arise. These could include, for example, interventions that require enormous investments and/or where it is clear in advance that (cost-) effectiveness or affordability will raise urgent questions. The central question here is whether society is prepared to – and able to – include these interventions in the basic insurance.

Cost-effectiveness is one of four package criteria that form the evaluation framework for package advice. These package criteria: effectiveness, cost-effectiveness, necessity and feasibility, are the direct "descendants" of the "Dunning Committee" criteria, for which it seems there was a large societal basis of support in the nineteen-nineties. This implies that healthy people feel a sense of solidarity towards sick people if:

- a serious health problem is involved;
- treatment exists that has proven its capacity for helping or ameliorating this health problem;
- the costs of the treatment are reasonably in proportion with the effects;
- the person responsible for these costs cannot bear these costs himself and society can.

These criteria have been elaborated upon in various editions of Package Management in Practice. However, development of these criteria is a constant process. For instance, we recently published an update of the assessment of the effectiveness criterion (the statutory name is Established Medical Science and Medical Practice) and we are currently elaborating further on the assessment of the burden of disease criterion (an aspect of necessity). In this section we elaborate on the cost-effectiveness criterion.

2.2 Cost-effectiveness in other countries

The same health care issues as in the Netherlands are also at play in the countries surrounding us. For this reason it is always useful to look at which basic criteria are chosen in other countries and within which process. In this case we paid specific attention to how they deal with cost-effectiveness.

From an international point of view, various organisations responsible for assessing the value of new technologies in their country have indicated a preference for using the QALY (e.g., England/Wales, Australia, Canada, Sweden). Most countries do not openly state to what extent they use cost-effectiveness. Slightly more is sometimes revealed during presentations at congresses. Indications are that an upper limit of

€45,000/QALY is applied in Ireland and an upper limit of €25,000/QALY in Hungary.

A study recently carried out within the framework of EUnetHTA, a European network for HTA organisations, provides information about the European situation. The study shows that most European countries (>90%) indicate including cost-effectiveness as a criterion in their assessments in order to arrive at a reimbursement decision on medicines.⁵ However, in practice the extent to which cost-effectiveness plays a really important role in the final reimbursement decision is often not clear. For instance, in large countries such as France and Germany, the decision on (the size of) a reimbursement is mainly linked to the size of a new medicine's relative improvement in effectiveness compared to that of the existing treatment, and cost-effectiveness plays (as yet) a limited role.⁶ Few data are available on most other European countries. A recent study of five European countries (Austria, Belgium, France, the Netherlands, Sweden)⁷ showed that, of these five countries, probably only in Sweden does the size of the added costs per QALY play a role in the ultimate consideration of whether or not to reimburse, but other factors, such as 'unmet medical need' (need for the treatment) probably play a more important role in this consideration.

Much less is known about the role of cost-effectiveness in assessing non-medicinal treatment. At the moment there are few signs that cost-effectiveness really plays an important role as criterion for reimbursement.

England and Wales form an exception to this. This is the reason why the Minister asked whether NICE could serve as an example for the Netherlands. NICE uses cost-effectiveness data for the assessment of both medicines and non-medicines. Moreover, England and Wales are most explicit about using threshold values. Partly as a result of this, the way in which NICE collects and uses cost-effectiveness data is often regarded as an example. In appendix 4 we provide a more extensive description of how cost-effectiveness is involved in decision-making in England and Wales. This paragraph will suffice by describing the main outlines.

A characteristic is that the NHS works within a pre-determined budget. The country is divided into regions in which the so-called primary care trusts (PCTs) have a budget. This means that the implementation of a new intervention in the NHS is at the expense of some other technology. In order to assess whether the extra costs of a new intervention are justified, NICE applies a threshold value between £20,000 and £30,000. Above this threshold value, the chance that something will not be reimbursed becomes increasingly greater. NICE has always used cost-effectiveness as a knock-out criterion in this way, whereby the point of departure is that every QALY has the same value, independent of the burden of disease. However, acceptance of this approach is dwindling. It has resulted in exceptions being made, for instance, for care in the final phase of life. In these cases, in addition to paying attention to cost-effectiveness, a link is also made with burden of disease.

Since January 2005 NHS organisations are obliged to reimburse medicines and treatment that NICE has recommended. In addition, NHS organisations have to comply with NICE's clinical guidelines. If NICE indicates that a specific technology has to be available for a patient population, the PCTs have to implement the recommendations within three months after receiving the advice. This mandate is

⁵ Kleijnen S, Goettsch W, d'Andon A, et al. EUnetHTA WP5: Relative Effectiveness Assessment (REA) of Pharmaceuticals. Background Review July 2011 (version 5B). <http://www.eunetha.eu>

⁶ Nooten F van, and Caro J. Use of relative effectiveness information in reimbursement and pricing decisions in Europe. *J Compar Effect Res* 2013; 2: 33-44.

⁷ Cleemput I, Franken M, Koopmanschap M, et al. European drug reimbursement systems' legitimacy: five-country comparison and policy tool. *Int J Techn Ass Health Care* 2012; 4: 358-66.

partly the result of a debate over post code medicine (the existence of differences between regions in the reimbursement of interventions). The fact is that various studies had revealed the existence of regional differences in the implementation of NICE advice, despite the obligation to comply. And this is despite the fact that NICE was actually set up to reduce geographical differences (post code medicine) in using new technologies.⁸

What can we learn from NICE? In the first place we must not forget that the UK has a different (government-funded) system. Furthermore, NICE has always used cost-effectiveness as a knock-out criterion, while here in the Netherlands we use several criteria. For the rest, NICE is currently also searching for a more sophisticated approach. Although the context of our two countries differs, so that the working methods of the UK cannot simply be adopted, NICE is justifiably regarded as an example. The soundness of their procedures, the systematic involvement of parties and clear communication about decisions can certainly serve as an example. For the rest, in some sectors similarities do exist between the two systems. For instance, a Dutch hospital could be compared with a PMT, as our hospitals are also restricted to a budget. When making its assessments, the Zorginstituut works closely with NICE and other European organisations. We see that similar discussions and problems arise in other countries and these can be solved in part by good international collaboration.

2.3 Cost-effectiveness in the Netherlands

Up till now, within the framework of our package advice, information we collected about cost-effectiveness was particularly (though not exclusively) for the assessment of (extramural) medicines. However, this information currently contributes little to reimbursement decisions. We can therefore understand the Minister asking us to elaborate on this criterion and its application. In this section, we therefore make proposals for making use of – and elaborating on – the cost-effectiveness criterion.

The key to the approach we propose is that we issue a basic statement on cost-effectiveness. It could be favourable or unfavourable. If favourable, then attention is paid to any other relevant considerations and whether “aggravating arguments” exist that argue against reimbursement. Naturally, it is always important to examine whether cost-effectiveness could be even more favourable.

If the cost-effectiveness is unfavourable, we will examine whether there are other relevant considerations that argue in favour of reimbursement. In effect, we weigh up all relevant arguments and on that basis draw up our ultimate advice. Within the framework of assessing cost-effectiveness, three questions are important, namely:

- Which requirements do cost-effectiveness data have to fulfil?
- How are cost-effectiveness data assessed?
- How do we arrive at a statement about whether the cost-effectiveness is favourable or unfavourable? Which values are taken into consideration and how do we assess the quality and uncertainty of information about cost-effectiveness?

2.3.1 *Requirements made of cost-effectiveness data*

Research data must be available to be able to assess cost-effectiveness. In the past the Zorginstituut drew up guidelines for pharmacoeconomic research. These

⁸ Drummond M, Sorenson C. Nasty or nice? A perspective on the use of health technology assessment in the United Kingdom. *Value Health* 2009; 12 Suppl 2:S8-13.

guidelines address all sorts of topics, such as which costs need to be included, how outcomes can be modelled, which perspective should be used, etc.⁹. The guidelines were drawn up from the perspective of society. This means that not only costs and effects within health care are included, but also those outside (reduced absenteeism, reduced WIA¹⁰-influx, travelling costs within the context of treatment etc.).

Up till now these guidelines only apply to medicines, as economic evaluation was only obligatory for the assessment of medicines (in some cases). However, the Zorginstituut feels it is also important to examine the cost-effectiveness of non-medicinal treatment. Although there is often a lack of research, it is in any case important to broaden the guidelines for health-economic research. With this in mind, we are revising both the existing pharmacoeconomic guidelines and the existing assessment framework for cost-effectiveness studies.

At the moment a pharmacoeconomic assessment is currently carried out using three different sets of guidelines, namely the guidelines for pharmacoeconomic research, also referred to as the Pharmacoeconomic (PE) guidelines (2006), the outcomes research manual (2008) and the cost manual (2010). Apart from the fact that using these guidelines simultaneously can be confusing, these guidelines are not always really appropriate for economic evaluations of non-medicines.

Taking all these things into consideration, this was sufficient reason for us to work on developing new guidelines that combine all available Dutch guidelines, makes unequivocal recommendations and which can be used broadly for health-economic research. There are two elements to the new guidelines, namely the main body document containing recommendations on how an economic evaluation should be carried out and a manual containing several in-depth modules. The purpose of the in-depth modules is to go into more depth on a select number of sub-topics by providing more explanation and/or instructions about specific recommendations in the main body document.

A temporary committee supported the Zorginstituut in revising the current guidelines. This committee was comprised of various experts many of whom already had seats on one of the Zorginstituut's package advisory committees. The committee was chaired by Prof. Maarten IJzerman, professor with the University of Twente. The updated guidelines were published in February 2016.

2.3.2

Assessment of cost-effectiveness data

When assessing cost-effectiveness, the Zorginstituut currently limits itself to a statement as to whether it has been sufficiently substantiated or not. A lot of important information is lost with such a statement. For instance, various reasons may result in a "negative" assessment. The data could be of insufficient methodological quality, or there could be too many uncertainties surrounding the data. We feel it is important to make such a distinction in the future in order to be able to issue statements that are more "overreaching" on the matter of cost-effectiveness. This will make cost-effectiveness data more effective in supporting decisions. This is important because nowadays the Zorginstituut has far more policy instruments at its disposal for linking consequences to its statements on cost-effectiveness.

This is why, henceforth in its cost-effectiveness assessments, the Zorginstituut will

⁹ Reference to pharmacoeconomic guidelines

¹⁰ WIA = Work and Income Act [unemployment benefits].

pay attention to the following questions:

1. Does the cost-effectiveness analysis have sufficient methodological quality?
2. What relationship exists between the ICER (incremental cost-effectiveness ratio) and a reference value?
3. Is the uncertainty about the ICER acceptable?
4. Would more research be useful and is it possible?

Re 1: When the conclusion is that the cost-effectiveness analysis (KEA) is of insufficient methodological quality, then the expected ICER can only be estimated. If the KEA is of sufficient quality, then the ICER can be assessed.

Re 2: In order to determine the place of cost-effectiveness, it is important to choose a reference value. Many misunderstandings exist about naming certain values, because people often think a decision is made on the basis of only a single value. A reference value is certainly not intended as a cut-off value for a reimbursement decision, but for determining a point of departure.

The question is, however, on what should such a reference value be based. Because cost-effectiveness is a relative value, ideally you would want to compare the ICER with the alternative: between which two interventions are you expected to choose? Often, however, the choice is not presented clearly. This is why we choose an absolute statistic. This is not a maximum amount that we will allow for an intervention, but the maximum difference permitted between the old treatment and the new one.

Various possibilities exist for such a value. For instance, the WHO has proposed values (1x GDP, 2xGDP and 3xGDP), the Health Council of the Netherlands proposed an ICER of €20,000/QALY as a cut-off value for vaccinations in the National Vaccination Programme and in 2006 the Council for Public Health and Health Care (RVZ) proposed using a maximum reference value of €80,000/QALY (with a maximum burden of disease) for package decisions.¹¹ This value was derived from sums for life insurance, from 3x Gross Domestic Product (GDP), and from what was used in other disciplines (e.g., water management). It all came out at about €80,000/life-year.

In order to determine the best amounts for reference values, you could take the amount that the average resident is prepared to pay for health care. This is known as "Willingness to Pay" (WTP). Research in the Netherlands has shown that, on average, the public would be willing to pay a maximum of €53,000/QALY on health care for another person. The sum is slightly higher if the care is for themselves or their relatives, namely €83,000/QALY. The reference values €50,000/QALY and €80,000/QALY have been adjusted to tally with these. The lowest reference value, €20,000/QALY, is the value that the Health Council of the Netherlands uses for the National Vaccination Programme and which the National Institute for Public Health and the Environment uses for prevention.

The amount the public are willing to pay for treatment is a way of looking at how high the reference value can be. Another way is to look at the opportunity costs. This is care that is not given when a new treatment is chosen. Recently published research from the UK shows that if reference values were to be based on opportunity costs (in the UK), they would amount to £12,936/QALY (€17,544/QALY). No such research is available yet in the Netherlands, and in view of

¹¹ http://www.rvz.net/uploads/docs/Achtergrondstudie_-_Zicht_op_zinnige_en_duurzame_zorg.pdf

the differences in, e.g., cost prices, it is difficult to base our reference values on this. However, in the future it may be possible to adjust reference values based on opportunity costs. N.B. This is a different approach to "Willingness to Pay", i.e., what the public is prepared to pay.

The Zorginstituut realises that a chosen value may raise questions. At the moment, in our elaboration we have taken as a basis the range proposed by the Council for Public Health and Health Care, i.e., €10,000 to €80,000/QALY. These values have become fairly well assimilated into the discussion on cost-effectiveness in the Netherlands and to date there seems little discussion about their substantiation. In the future, these values can of course be adjusted if there is reason to do so.

The Zorginstituut feels it is a justified point of departure to allow higher costs per QALY when a high burden of disease is involved. Research has shown that this too can count on societal support¹². This means that lower reference values will be used when a lower burden of disease is involved. We have discussed with the parties¹³ possible scenarios and reference values for the assessment of cost-effectiveness. They indicated a preference for linking reference values with 1xGDP, 2xGDP and 3xGDP. This is so that reference values can also be adjusted in the future, if costs rise, e.g., due to inflation. Allowing this assessment to take place annually would lead to fluctuations. It is therefore desirable to allow such an assessment to take place not annually but once every 5 or 10 years. In addition, the parties suggested not only a connection between costs per QALY and burden of disease, but also with the effect size. We feel this would be incorrect, however, because the effect size is already taken into account when assessing the therapeutic value. For the rest, the effect size will carry weight in societal assessment of all arguments (see the next section).

In our country discussions are still taking place about how the burden of disease should be calculated. Various methods exist for this. Some people favour a "proportional shortfall"-approach, whereby the threat of health loss is related to the remaining (quality-corrected) survival. The loss of a year weighs more heavily for a very old person than for a child so that this approach discriminates in favour of the elderly. Others feel more for the so-called 'fair innings' approach, that takes into account that very old people have already enjoyed many more life-years than young people. Another approach is based on the life-threat presented by a disorder (rule of rescue).

As we have not yet agreed on how to calculate burden of disease, for the present we will use the 'Global Burden of Disease' data of the WHO. This calculation is based on Disability-Adjusted Life-Years (DALY). A DALY includes morbidity and mortality in an index by adding the number of life-years with a disability to the number of life-years lost. The Zorginstituut has prioritised solving the matter of how to calculate burden of disease and will publish on the matter in 2016.

In 2006 the RVZ proposed using a curve in which the costs per QALY and the burden of disease are set off against one another. The curve included a diagonal line representing €10,000/QALY for a burden of disease of 0.1 for up to €80,000/QALY for a burden of disease up to 1.0. In principle, interventions below the diagonal line should be reimbursed; interventions above it should not. The RVZ included the reservation that this principle-based decision can be corrected for reasons of

¹² CBS research on solidarity preferences in care, 2015/5

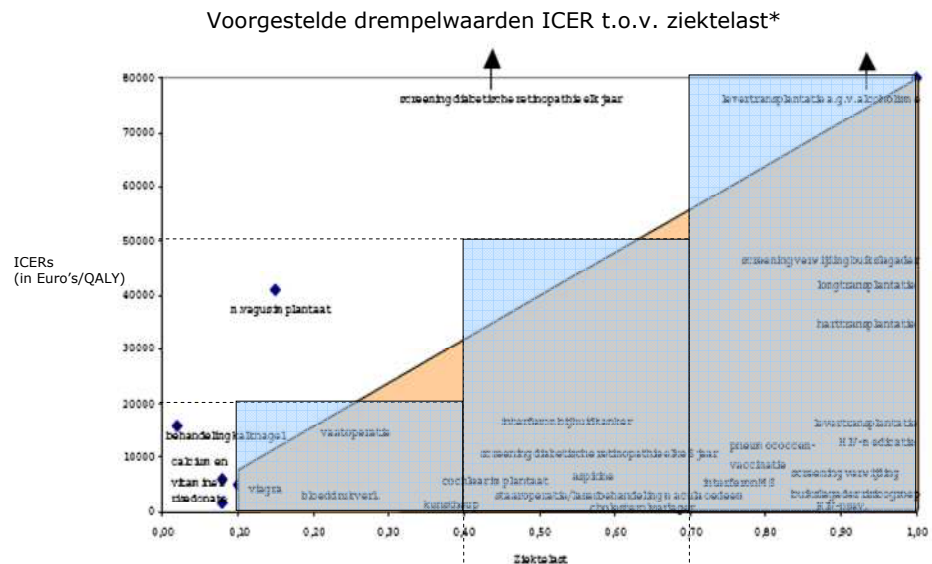
¹³ Invitational conference with parties on 2 October 2014. The report of this meeting is enclosed with this report as appendix 1

solidarity and justice. An important difference between the approach suggested by the RVZ and the approach we suggest is that the values do not serve as limits or ceiling values, but as reference values.

The Zorginstituut wants to work within the bands €10,000 to €80,000/QALY with three corresponding categories of ICER and burden of disease instead of a curve. This is because we have to cope with both a point-estimate of the cost-effectiveness and the burden of disease, thus also with the uncertainties these involve. This problem is largely solved by working with classes instead of a curve. The classes are as follows.

Burden of disease	Maximum additional costs (€) per QALY
From 0.1 up to and including 0.4	Up to €20,000 per QALY
Between 0.41 and 0.7	Up to €50,000 per QALY
Between 0.71 and 1.0	Up to €80,000 per QALY

The following figure describes the relationship between the three proposed classes and the curve proposed by the RVZ.



*Dit is een aanpassing van de grafiek uit het RVZ rapport van 2006

The following applies when assessing these values. The closer the estimated ICER of a treatment is to the reference value, the better the methodological quality has to be (see re 1) and the smaller the uncertainty regarding the ICER is allowed to be (see re 3). If the ICER of an intervention is higher than the reference value, the Zorginstituut can conclude that the intervention is probably not cost-effective. One

difference with the RVZ's proposal is that no principle-based decision takes place based on an assessment of the reference values. If the value is within the field, the colour changes to green, if it is outside the field, then it changes to red. This is not necessarily a reason for non-reimbursement, but it is a reason to take a critical look at the cost-effectiveness.

Re 3: It is important to know whether sufficient certainty exists surrounding this ICER in relation to a reference value (see point 2) or whether it would be useful to carry out supplementary research (see point 4). It is possible to make a 'Cost-Effectiveness Acceptability Curve' (CEAC) with the help of the results from a so-called Probabilistic Sensitivity Analysis (PSA). A graph will show, per reference value, what the chances are that a treatment is cost-effective at each specific reference value. Whether the degree of uncertainty is acceptable depends on a number of factors, such as, e.g., whether large investment costs are necessary and whether these are irreversible. This is mainly a policy consideration that the Zorginstituut has to weigh up. If the uncertainty is not acceptable, a further (policy) consideration is whether further research would be useful and is feasible.

Re 4: If it turns out that the ICER is surrounded by a lot of uncertainty, then the question is whether more research can remove this uncertainty. Relevant to this (particularly for ICERs close to the critical reference value) is the question of whether the missing data have a major impact on the ICER. It is also important to assess whether (proposed) research will actually result in the supplementary information.

More research can lead to more certainty about the value of the 'true' ICER, and therefore reduce the chance that an incorrect conclusion is drawn. Univariate deterministic sensitivity analyses and 'Value of Information' (VOI) analyses can play a role in determining which parameters have a major impact on the ICER and are critical to the cost-effectiveness analysis. It is possible to weigh up whether supplementary research is necessary and useful based on such an analysis.

Once the critical parameters have been determined, it is possible to assess whether the relevant information can be collected within the foreseeable future. This involves taking a look at a number of methodological aspects. If the ICER is strongly influenced by the price of treatment, then follow-up research into cost-effectiveness will only have a limited value. After all, research is intended to reduce uncertainty and the price of an intervention is not a source of uncertainty that research can rectify. Where the costs are high or the ICER is unfavourable, it is better to focus on limiting the volume or on reducing the price than on carrying out more research. We discuss this in more detail in the following paragraph.

2.3.3 *Policy instruments that can affect cost-effectiveness*

We mentioned earlier that nowadays the Zorginstituut has more instruments for linking consequences to their assessment of effectiveness and cost-effectiveness. This has introduced alternatives to the "classic unequivocal, definitive yes/no decision". The instruments are as follows:

1. Reimbursement *and* research
 - a. conditional admission of treatment/care, the effectiveness of which has been insufficiently established on a group level;
 - b. conditional funding of treatment/care if the cost-effectiveness has been insufficiently established and research results could affect the reimbursement decision within the short term;

2. Cost-effectiveness can be improved by means of agreements about outcomes ('performance-based'); by making agreements about start and stop criteria, on maintaining a register of results, and by setting up indication committees. Or agreement can be reached that reimbursement will be at the expense of the manufacturer if a certain cost-effectiveness is not achieved for individual patients.
3. Financial agreements; these could relate to price, but also to the total budget, or a price-volume deal, whereby the price is reduced if the volume increases.

Conditional admission will only take place if care is not part of established medical science and medical practice, i.e., its effectiveness is (as yet) unproven. Relative effectiveness on a group level has already been established for the other arrangements. The word arrangement is appropriate in that it indicates the involvement of customisation, whereby the objective and the means have to be meticulously determined by the parties involved. The various perspectives are automatically brought to the table when designing and implementing arrangements. The outcome of an arrangement does not always have to involve an explicit alteration in the package; the positioning of a new form of care can also be included in the treatment guidelines or in a consensus document.

These instruments are still at the development stage, both within the Zorginstituut and the Ministry, as well as internationally. The goal is to deploy the right instrument (alone or in combination) in the right case and in such a way that any risks signalled are controlled. An example of such a risk could be influencing an unfavourable cost-effectiveness to make it favourable so that it does fall within the appropriate classes.

Experience has taught that a decision to follow a conditional path must also be made meticulously. After all, it may be the case that the necessary information will not be generated or that it does not confirm the favourable prospects. Removing an intervention to which people have already become accustomed from the package is more difficult than not allowing it to enter the package (conditionally). Another question that arises is about the relationship between a conditional path and an assessment of all package criteria; this is discussed in the following section.

3 Cost-effectiveness and package management: societal considerations

3.1 Framework for societal consideration

A package assessment is where all information about an intervention and the situation in which it will be used are brought together. The information supplies the ingredients for all relevant arguments that have to be weighed up against one another. The Zorginstituut carries out a preselection process regarding the discussion carried out by the Insurance Package Advisory Committee. This committee is made up of members appointed by the Minister in order to assess the societal implications of package advice. The committee advises the Zorginstituut's Executive Board. It does this on the premise that the basic insurance is an obligatory insurance for which all citizens pay. This solidarity has to be safeguarded. This means there must be very good reasons for including an intervention in the package. This is why the following questions are always in the background:

1. What happens when an intervention is not included in the package?
2. Are people losing out because they are not (or no longer) receiving an intervention because a different intervention has been chosen for inclusion in the package?

Re 1: The Zorginstituut's point of departure is that citizens are insured for good care, no more than is needed and no less than is necessary. The Zorginstituut's basic idea is therefore that an intervention will not be included in the insured package unless there are good reasons for its inclusion. These reasons can be found in the public preconditions: quality, affordability and accessibility, which have been elaborated upon in the package criteria necessity, efficacy, cost-effectiveness and feasibility.

Re 2: Complementary to the question of what the consequence could be for patients with a certain disorder when an intervention is not included in the package, is the question of what this could mean for patients with other disorders. Are they running the risk of not (or no longer) receiving reimbursement because – after all – the money can only be spent once? In the introduction we mentioned the fact that answering this question is difficult at the moment because the package question is currently always about one individual intervention and not about the choice between two or more interventions within a pre-defined budget. This is why we do not propose using cut-off points that can serve to make a choice between two interventions, but using reference values that give an idea of the added value of an intervention relative to the usual alternative.

These are the questions at the back of our minds when we collect data on package criteria in order to gain insight into a situation. What is the disorder precisely? What does this mean to the patient? Is it serious? What does the proposed treatment do to help this and what does it cost to realise this effect? Can the patient bear the costs of treatment him/herself? Can society bear all the costs of treatment? A societal appraisal maps and weighs up all this information. Of all these criteria, only effectiveness is automatically decisive. The implication is that care that fails to fulfil this criterion is not regarded as insured care. This is explicitly stipulated by law with the help of the criterion "Established medical science and medical practice". We explained how we assess this in the report "Assessment of established medical science and medical practice". A crucial aspect is that the effectiveness of treatment

has been sufficiently substantiated based on outcome parameters that are regarded as relevant. In our report we demonstrated that such an assessment is customised, and close attention is paid to the substantiation – which will, ideally be – provided. If the outcome of the assessment of effectiveness is positive, we then examine the cost-effectiveness as described in the previous section. This results in a statement about whether the cost-effectiveness is favourable or unfavourable. This statement is placed alongside all (other) arguments for determining whether they justify accepting higher or lower costs per QALY. This could include a discussion of certain elements from the effectiveness assessment (such as the size of the effect, how the effect is divided over the group and the probability of the effect) and from the cost-effectiveness assessment (size of the burden of disease, probability of the ICER etc.). It is important that all underlying arguments of these assessments are included in the societal appraisal phase.

Although the package criteria are quite clear in themselves, and they can count on societal and political support, it is important that they are used consistently and transparently. After all, when is a health problem serious? When can a person be deemed responsible for paying their own costs of treatment? These are not questions that can be simply answered with a yes or no, or with a concrete number or sum. In effect, using these criteria is not a mathematical process with yes/no outcomes. This would mean the final assessment was a simple case of adding up the pluses and the minuses. In reality matters are much more complex. The societal context plays an important role in all this.

This is why the parties are involved in our advice at an early stage in order to involve all relevant information and arguments. The Zorginstituut's advisory committees (WAR and ACP) are also increasingly collaborating in order to harmonise, early on in the process, societally relevant topics such as outcome measures and the choice of standard treatments.

In this context arguments may come to the table that cannot exactly be regarded as falling under these package criteria. This is why room is always needed for introducing new societal arguments. Various sources describe arguments that should be examined in combination with the cost-effectiveness criterion. Firstly, what is stated by the RVZ in its report "Appropriate and justifiable health care" (RVZ, 2007, page 22). The RVZ indicates that societal arguments which can play a role include: burden of disease, personal responsibility, societal ancillary effects, the temporary nature of interventions, rarity and budget impact, and uncertainty about the amount of costs involved.

A second source is the research that Jan van Busschbach¹⁴ carried out at the request of the Zorginstituut (still CVZ at the time), partly in response to the RVZ report, into criteria that play a role in decision-making in combination with cost-effectiveness. He named both arguments that make the cost-effectiveness requirement milder and arguments that do the opposite. Arguments that are thought to make the requirement milder are: a high burden of disease, rarity, consequences for informal care and risks to public health. Arguments that are thought to make the requirement stricter are: little overlap with the health care domain, high budget impact, failing to include future costs, unsuitability for insurance and uncertainty about the appropriateness.

A third source are the GPS guidelines (Guidance on Priority Setting in Health Care) that came about on the initiative of the "Unit for Costs, Effectiveness, Expenditure

¹⁴ J.J. van Busschbach. G.O. Delwel. The cost-effectiveness package principle, background study to assist the 'appraisal' phase in package management, CVZ, 2010 (publication number 291)

and Priority-setting (CEP) of the WHO. The guidelines present considerations for and against reimbursement, categorised into four different domains (relating to, respectively, disorder, social groups, protection against financial and social effects of bad health and other considerations) in addition to the cost-effectiveness criterion. What is noticeable is that all the criteria have an 'equity' approach: is the patient better off in terms of health or social economic status than the 'average' patient either in the past, the present or in the future? In effect, using these criteria gives priority to patients who can be treated less cost-effectively, at the expense of normal, average patients.

The above-mentioned list shows that many of these arguments, though not all, are covered by the package criteria. It is also the case that arguments are mutually dependent. For instance, a high burden of disease can be an important consideration, but if the intervention has a low effectiveness, it will not provide a patient much in the way of health gains.

Researchers at the University of Twente are currently researching whether the Multi-Criteria Decision Analysis (MCDA) method can play a supporting role in the Insured Package Advisory Committee's societal appraisal. To this end, they are also doing retrospective research to examine which arguments to date have played a role in the ACP's advice. MDCA is an instrument for supporting decisions in which multiple and conflicting arguments play a role. The results of the study will be processed in the assessment framework that the Zorginstituut is drawing up. The objective of this assessment framework is to increase transparency:

- which considerations play a role;
- what relationships exist between these considerations;
- what is done with uncertainties and methodological vulnerabilities;
- where in the process are these considerations made, also in relation to deploying such policy instruments as conditional admission and funding, and agreeing on arrangements.

We will of course involve the parties in health care in developing this assessment framework. We plan to publish this framework at the end of 2016.

3.2 **Is statutory anchoring of cost-effectiveness desirable?**

An important question is whether laws and legislation are necessary in order to use the proposed method of working.

The basic package has on the whole been given an open definition. All care must be effective. This is regulated by law as an inclusion criterion. An intervention that does not fulfil this criterion cannot be regarded as an insured benefit. The minister has also asked the Zorginstituut to make proposals for the statutory anchoring of the cost-effectiveness criterion.

The package criteria on which we base our advice to the Minister of VWS about the contents of the basic package should be regarded as a perspective-orientation guide for our advice. The package criteria have a solid historical basis and have also been accepted by the legislator as is apparent from the explanatory text on the Health Insurance Act (Zvw). When the Zvw was introduced, the decision was made not to anchor it in the law.¹⁵ The involvement of package criteria in our advisory task does

¹⁵ When the Zvw was drawn up, a discussion did take place about statutory anchoring of the criteria for determining the contents of the basic insurance. In an amendment, such a proposal was rejected by the Lower House. The Explanatory Memorandum does state: "The government concludes that the package to be insured under the Zvw

not necessarily demand statutory anchoring. Even without a statutory basis, we can formulate our advice on inclusions and removals based on an assessment of the package criteria.

Nevertheless, we think it is desirable to statutorily establish that the package criteria should serve as the basis to our advice to the Minister about the contents of the basic package. This is in order to confirm the societal and political basis of support for the package criteria. Nor is it without significance from a legal point of view. Involving the package criteria in our advice on the contents of the package is more mandatory. We recommend not limiting the regulation. After all, this would preclude in advance, and by definition, that the Zorginstituut could also involve other considerations in its advice.

The VVD-PvdA Coalition Agreement dated 29 October 2012 includes the proposal to statutorily anchor cost-effectiveness. This indicates a political desire to allow cost-effectiveness to play a more prominent role in package decisions. This greater role will be realised by statutorily regulating the involvement, in principle, of cost-effectiveness in our considerations when advising on the contents of the basic package. As mentioned earlier, because advising on the basic package involves an integral weighing up of all relevant arguments and circumstances, the Zorginstituut feels that realisation of this statutory anchoring should not be limited to cost-effectiveness, but should include all package criteria.

For the sake of good order, we would add that it is possible that what the writers of the coalition agreement had in mind was to include the concept of cost-effectiveness as part of the definition of a provision (i.e., as with the concept of 'established medical science and medical practice'). In order to demarcate, or respectively limit, the contents and size of the insured package, the Health Insurance Decree states that care only falls under the basic insurance if it fulfils the 'established medical science and medical practice' criterion, i.e., if the care can be regarded as effective. The question is then raised as to whether the concept 'cost-effective' should be added to the definition of a provision under the Health Care Decree. This requires that a short summary is included in the Health Care Decree that care is only included in the basic package if it fulfils the 'established medical science and medical practice' criterion (is effective) and is cost-effective. We believe that this is not the right route to take, as enormous objections exist to such a statutory anchoring:

- Cost-effectiveness is not an unequivocal concept that can be operationalised easily. It can lead to all sorts of differences in interpretation and for this reason the concept cannot be used as a description for demarcating the insured package.
- The lack of cost-effectiveness data would 'automatically' lead to the conclusion that an intervention is not included in the package, even in a case of an effective intervention. For most forms of care, no data, or insufficient data are available to be able to assess (cost-) effectiveness. This means it is impossible to determine whether most of these provisions should be included in the basic package, or worse still: little would remain in the basic package.
- This would make cost-effectiveness an isolated knock-out criterion, which is not

must relate to necessary care, assessed for proven effectiveness, cost-effectiveness and the need for collective funding. In realising this, the government adhered to the criteria of the Dunning committee. This guaranteed equal accessibility and solidarity in health care. This meant that the contents of the package are the outcome of a political assessment that also took into consideration the affordability of the system in the long term. (...) It also means that the insured package needs continued assessment. I regard this task as ideally suited to the College voor zorgverzekering. See the Explanatory Memorandum with the Zvw, page 24.

in line with how the Zorginstituut operates. In this report we have clearly shown that all criteria are subjected to an integral evaluation, which argues against this option.

3.3 Package-wide application

In the various editions of Package Management in Practice, we have indicated a desire to make broad use of the assessment framework. This implies assessing cost-effectiveness in fields where this does not currently take place, e.g., long-term care and curative care. Up till now cost-effectiveness was mainly assessed for package advice on (extramural) medicines. This relates to the way in which access to this care is regulated by law. After all, an open definition applies to most of the package. A closed definition applies to extramural medicines. This means the Minister can impose additional requirements in relation to inclusion. Requirements relating to cost-effectiveness also apply to medicines. These now apply to expensive intramural medicines too (which are part of the open definition of care provided by medical specialists). This is why a lot of cost-effectiveness data are available for assessing medicines. Furthermore, this involves a clear role for manufacturers who are obliged to supply these data.

The Zorginstituut issues outcomes of assessment within the framework of openly defined care. This is where they determine, on their own initiative or after being asked, whether the care involved fulfils the established medical science and medical practice criterion. For some time the Zorginstituut has included a cost-consequence estimate or budget impact analysis in its assessments of outcome. This is where we estimate which costs are involved in the reimbursement of care, or which costs will be avoided in the event of a negative assessment.

In view of this report, the next logical step would be to discuss the assessment of cost-effectiveness in the outcomes of assessment that we issue. Clearly, this must be done efficiently. This means that we will do this for outcomes of assessments where we envisage risks. This is in keeping with the criteria for risk-based package management that we apply when assessing medicines. This implies that the budget impact must be higher than 2.5 million euro and/or that risks exist relating to efficacy, safety, a rapid introduction, etc.¹⁶

3.4 Examples from daily practice

To provide an idea of how the Zorginstituut's work would look, we will discuss two examples: an intervention that falls under care provided by medical specialists and a specialist medicine.

3.4.1 *Left Ventricular Assisting Device (LVAD)*

The Zorginstituut recently issued a positive assessment of outcome on the LVAD that included a number of considerations about its cost-effectiveness and the measures to be deployed.

In the Netherlands, LVADs (support hearts) are used on patients with severe heart failure, to bridge the time they spend waiting for a heart transplant (bridge to transplant), but also as destination therapy. In 2007 the Zorginstituut issued a negative outcome of assessment about the support heart as destination therapy. In view of the rapid development of support hearts in recent years and the availability of new literature, we recently issued a new (positive) outcome of assessment, with a number of marginal comments.

¹⁶ For a description of the criteria, see: Risk-based package management: the assessment of extramural medicines and the report on assessment procedures for specialist medicines

The LVAD is a mechanical pump that is introduced into the chest or abdominal cavity. The LVAD is indicated as destination therapy for patients with final stage heart failure who are not eligible for a heart transplant. Heart failure is a reduced pump function of the heart, as a consequence of, e.g., a heart infarction or a congenital heart disorder. The symptoms include reduced exertion tolerance, shortness of breath and tiredness. Severity is usually expressed in terms of NYHA classes I–IV. The prevalence of heart failure in the Netherlands rises sharply with age.

Assessment of effectiveness

The assessment shows that, in comparison to conservative treatment, the LVAD leads to a significant survival advantage, an improvement in the NYHA class and the 6-minute walking test and an improved quality of life. The results varied per type of pump. Implementation of the LVAD does lead to more incidents than conservative treatment (haemorrhages, infections, CVA, the biggest risk within a month after implantation). Taking everything into consideration, the Zorginstituut concluded that for this indication the LVAD as destination therapy is established medical science and medical practice.

Assessment of cost-effectiveness

In a relatively optimistic scenario the cost-effectiveness of LVAD implementation as destination therapy in comparison to optimum medical treatment amounts to, on average, €107,600 euro per quality-adjusted life-year gained. Cost-effectiveness would be influenced favourably if the price were lower and/or if the number of complications could be reduced.

Assessment of burden of disease

This is a serious disorder. 35% of patients die within one year of being diagnosed. It can be assumed that the burden of disease is enormous. A calculation based on the proportional shortfall method results in a figure of 0.717.

An assessment against the reference values for the highest burden of disease category (which is where 0.717 can be found) shows that the cost-effectiveness must be deemed unfavourable. This is mainly to do with the number of complications that occur. The Zorginstituut has therefore agreed with care providers that:

- The care providers will draw up a consensus document in which the indication criteria for LVAD will be recorded;
- the indication will be labelled as multidisciplinary;
- all patients who receive an LVAD will be registered and the registration data will be evaluated regularly. On the basis of these, it will be possible to adjust the indication criteria in the consensus document if necessary;
- only care providers with expertise may implant the LVADs.

As the agreements were only made recently, it is not yet possible to state whether they have contributed to a reduction in complications and thus a more favourable ICER. The Zorginstituut is following the number of LVADs implanted for this indication. An unexplained increase in the number of implants could form a reason for getting back to the professional group. If the effectiveness, and thus the ICER, does not improve with these measures, the next step could be to assess whether the treatment should be removed from the package. All other considerations will also play a role here, such as the argument that this treatment is the only treatment option for most patients.

3.4.2 *Pirfenidon (Esbriet®)*

Another example is the assessment of pirfenidon (Esbriet®). Esbriet® is an orphan drug that can be prescribed for patients with the severe disorder idiopathic lung fibrosis (IPF). This drug seemed effective for some patients. The cost-effectiveness was insufficiently substantiated; expectations were that it would be unfavourable. We opted to use both a financial arrangement and to make agreements about determining the indication. The financial arrangement can improve the total costs and/or costs per patient. The idea behind the indication protocol was to limit access to patients who will benefit. By using both instruments, we are making both the numerator (costs) and the denominator (effectiveness) more favourable, so that they fall within an acceptable margin and the treatments can continue to be available.

This examples clearly illustrates how a new question arises, namely when is unfavourable cost-effectiveness a decisive reason for saying “no” and when is it a reason for making use of an instrument. It is important, right from the start, to obtain as many guarantees as possible that a trajectory will be completed successfully. Within the context of weighing up, we will try to maintain as clear a picture as possible of the applicable criteria.

3.5 **Contribution of the parties towards providing cost-effective care**

The examples in the previous paragraph really demonstrate what contributions the parties can make to cost-effective care. Making agreements between patients, care providers, health insurers, hospitals, manufacturers and the government about indications, prices, research, registration, etc., allows an intervention to score as favourably as possible on cost-effectiveness and therefore become available – or remain available – for patients. What we must realise, however, is that something which is cost-effective on a government level (macro) is not necessarily cost-effective on other policy levels. For instance, a hospital has a different perspective from the government, which could result in other motives playing a role in a decision, such as, e.g., the perspective of competition when purchasing new medical technology. On a micro-level, in consultation rooms, cost-effectiveness looks quite different. The choice of care providers and patients will no longer be limited to a possible added value of treatment, but will also depend on the individual circumstances and preferences of patients.

The Zorginstituut will pay attention to this when revising its health-economic guidelines. Just as with the current guidelines, the new guidelines indicate that an economic assessment must be carried out from the perspective of society. In addition, a new piece of text has been added, stating that the results can also be reported from the perspective of health care. There will also be a separate section discussing the details of a number of fields of application that, other than with medicinal care, form an exception.

The increasing cost-awareness of the parties increases the chance that cost-effective care will be provided. The treatment guidelines of care providers play an important role here. This is the topic of the next section.

4 Treatment guidelines and cost-effective care

A lot of care that is provided in the Netherlands is described in treatment guidelines. This is important for the quality of health care. In principle, guidelines are based on the stepped care principle. This means that the first treatment used is that which is least invasive and which works in many cases (and is often also the cheapest). Professional guidelines have traditionally been the domain of the professional group. Currently, however, it is often the case that patients are involved in the guidelines and that more multidisciplinary guidelines are being drawn up. The responsibility of the Zorginstituut in the field of quality is to encourage the development of care standards. These are guidelines that describe the care content, the care process and relevant indicators, and which are jointly developed and provided by patients, care providers and health insurers (tri-partite). Care standards and professional guidelines are increasingly paying attention to the substantiation of recommendations with cost-effectiveness data.

4.1 A brief history of guidelines and cost-effectiveness

At the end of the nineteen-nineties, the then Minister of Public Health gathered together a large number of parties (CBO, iMTA, OMS, NHG, NPI and organisations of paramedics) in a programme, the aim of which was to collect cost-effectiveness data into clinical guidelines. This was to support individual care providers when drawing up an effective treatment plan. The consensus on 'Cholesterol' subsequently included a formal cost-effectiveness analysis for the first time.^{17 18} This raised the following question: what is an acceptable relationship between effects and costs? And: who can and should be responsible for determining this? Questions that are still being asked.

In order to reply to the first question, the consensus document claimed that recommendations on medical grounds were also acceptable in respect of cost-effectiveness as long as the NLG40,000 (18,151 euros) limit per life-year gained was not exceeded. A reply from Casparie et al.¹⁸ to the second question was "that responsibility rests not only on the government: doctors must also attempt, when making decisions for their individual patients, to arrive at the most cost-effective possible method of treatment and at a reasonable, though not explicitly named, balance between the effects and costs of their actions".

Involving cost-effectiveness considerations in the development of guidelines did indeed result in a discussion¹⁹. From a legal point of view, taking financial consequences into account (as well as other non-medical aspects) is compatible with the statutory rules for effective medical action.²⁰ It becomes complicated, however, if a care provider ignores better care merely due to higher costs; this could conflict with their professional standards. At the same time, societal responsibility is also one of the non-professional context-related aspects of those professional standards. Another argument supporting the use of cost-effectiveness data is that choices have to be made irrespectively; this should preferably be done on a rational basis and

¹⁷ Simoons ML, et al. The treatment and prevention of coronary disease by reducing the serum cholesterol concentration; third consensus 'Cholesterol'. Ned Tijdschr Geneesk 1998; 142: 2096-2101.

¹⁸ Casparie AF, et al. Guidelines and costs. Ned Tijdschr Geneesk 1998; 142: 2075-2077.

¹⁹ Stehouwer CDA. Policy advice to doctors and economic considerations involved; benefits and objections. Ned Tijdschr Geneesk 1999; 143: 776-778.

²⁰ Gevers JKM, Biesart MCIH. Medische beslissingen, kostenoverwegingen en richtlijnen voor medisch handelen; kanttekeningen van uit het recht. Ned Tijdschr geneesk 1999; 143: 2629-2632.

transparently.

The conclusion in the various publications was “that financial considerations play a role in medical actions, but when these considerations conflict with medical-professional action, this is something that cannot be asked of a care provider. A decision will eventually have to be made by the government”. This conclusion clearly shows that various perspectives can exist alongside one another when making decisions about health care.

Since then the professional group came up with a number of initiatives in an attempt to link evidence-based medicine, cost-effectiveness and the dilemmas to one another. However, these initiatives were unsuccessful and were discontinued. Government institutions tended to clamp onto the idea of linking cost-effectiveness and medical guidelines to one another. For instance, in 2006 and 2007 the reports of the RVZ and the CPB, respectively, which argued in favour of involving cost-effectiveness considerations in the development of guidelines. The CPB report argued that cost-effectiveness as a decision-making criterion in package management was no use because the cost-effectiveness of an intervention largely depended on the characteristics of an individual patient. Partly due to this, the CPB argued in favour of involving the cost-effectiveness of new medical technology when drawing up guidelines, protocols and standards.²¹

Also the *Regieraad* (now part of the Zorginstituut) commented in its ‘Directive on guidelines’ (2010): “Insight into the financial consequences of recommendations is needed to be able to make societally responsible choices when spending resources on health care. It is important that major organisational and financial consequences of recommendations are discussed or calculated and that a statement is issued about them.”

Over the years, we seem to have come around to the idea of involving cost-effectiveness aspects in the development of guidelines. We have also seen in the meantime what the potential pitfalls are. For instance, there was often a lack of cost-effectiveness data because research cost too much and/or no-one would accept responsibility for undertaking research. Where data were available, no decision could be made based on them because of the lack of a norm, a threshold or a reference value. Furthermore, the proper expertise was often not available among (para)medics and structural funding was lacking for the extra work involved in developing guidelines.²²

Nevertheless, we have seen clear changes during the past few years. Under the pressure of the economic recession and increasing health care costs, professionals also find themselves increasingly confronted with the need to make choices in health care. This has resulted in new initiatives for including cost-effectiveness in guideline development.²³ We increasingly see that umbrella organisations for professional groups are searching for opportunities to provide cost-effective care where in the past the initiative came mainly from the government. This is a step in the right direction. It will also generate new knowledge and information that can fill the lacunas in knowledge about – and experience with – cost-effectiveness in guidelines.

²¹ CPB Document: QALY-time. New medical technology, cost-effectiveness and guidelines. Oktober 2007, no. 152.

²² Hakkaart L, Feenstra TL, Buskens E. Handboek evidence-based richtlijnontwikkeling Hoofdstuk 19 : Doelmatigheid in guidelines.

²³ For some time now the Dutch College of General Practitioners (NGH) has involved the costs of interventions in its recommendations in the NHG-standards, for example, by consistently choosing for generics instead of for brand names.

4.2 Existing and new initiatives

For some time initiatives have existed in the field of appropriate use. For instance, the parties are working on a number of topics within the framework of a "round table" covenant. This is where the parties make agreements on deploying certain care "with greater focus". Although cost-effectiveness is not the primary perspective here, these agreements can exert a positive effect on it.

A new initiative of the Federation of Medical Specialists (since 1 January 2015 the successor the Association of Medical Specialists) is that they want to give cost aspects a structural role in the guidelines for medical specialists. They want more transparency in the costs and results of health care and an estimate of whether the deployment of resources is in proportion to the health gains generated. They are exercising with this in a pilot, the so-called *Koploperproject* [Front-runner project]. What this amounts to is that cost details, including cost-effectiveness data, will be used to develop four sets of guidelines. The Federation will report on its experience with this project in the first six months of 2015.

The Zorginstituut regards this as a good development. It is providing the project with financial support, including a systematic review into suitable cost-effectiveness studies of interventions that will be proposed in guidelines on peripheral arterial venous diseases (PAV).

Developments are also taking place in the field of oncology. In oncology, the costs of (new) medicines are becoming a particularly acute problem and the discussion of limits to costs per life-year gained is very topical. The KWF recently issued a horizon scanning report on the accessibility of health care in relation to increasing costs.²⁴ In addition to a number of recommendations on national and European levels, as well as on the level of hospitals, the scanning committee also suggests that the BOM (*Beoordeling Oncologische Middelen*)²⁵ [Assessment of Oncological Resources] committee should take a critical look at the cost-effectiveness of every new medicine.

Lastly, cost-effectiveness aspects are involved as a matter of course in the development of guidelines on mental health care (GGZ).²⁶ The GGZ Network has asked the Zorginstituut for health-economic support for including cost-effectiveness considerations in the care standards that they will be supplying for inclusion in the Zorginstituut's register.

4.3 Can cost-effectiveness data in guidelines also be used for package management?

Although there is a lot of overlap between the aims of treatment guidelines and those of package management, differences may also exist. Nevertheless, it is useful to use the same cost-effectiveness data where possible. The Zorginstituut advises that guideline work-groups work according to the step-by-step plan described in the section "Cost-effectiveness in guidelines" in the "Manual on evidence-based guideline development, a guide for use in practice"²⁷. The advice and expert group on quality standards (AQUA), an advisory committee of the Zorginstituut, recently

²⁴ The accessibility of expensive cancer medicines, now and in the future. June 2014, KWF [Dutch Cancer Society] for combating cancer.

²⁵ The BOM committee was established by the Dutch Association for Medical Oncology (NVMO). The committee advises professional groups about the status of new medicines.

²⁶ www.ggzguidelines.nl

²⁷ Hakkaart L, Feenstra TL, Buskens E. Handboek evidence-based richtlijnontwikkeling Hoofdstuk 19: Doelmatigheid in richtlijnen.

drew up guidelines for drawing up such quality standards. The guidance cites 19 quality requirements. One of these requirements addresses economic aspects:

“Information on cost-effectiveness can be used to tighten up recommendations, to improve their substantiation or to differentiate according to specific sub-groups of care consumers. In addition to information about cost-effectiveness, information about the impact of the recommendations on a population level can also be extremely valuable for quality norms that focus on changing current practice. A so-called budget impact analysis will provide insight into the expected change in effects, costs and capacity utilisation on a national level and is necessary for possible choices that need to be made in health care. The role of this type of economic evaluation can also be a signalling one, in the form of bottlenecks that need attention in the event of implementation. A health economist can assess the quality of economic evaluations and their applicability to Dutch health care and contribute to integrating this knowledge effectively into quality standard recommendations. With all this, it is important to bear in mind that quality standards surrounding chains can be so complex that an economic evaluation is not feasible.”

The Zorginstituut would also like guideline developers to take into account the usefulness of their recommendations for package assessments. After all, in package management we look at the assessment of effectiveness and cost-effectiveness, as well as at current guidelines or care standards. Although the Zorginstituut realises that the perspective of the individual treatment of a patient may differ from that of the collective basic insurance, it is good to generate information for both perspectives where possible. An important point for attention here is that foreign data cannot automatically be used for the Dutch situation. After all, these may differ on one or more points, such as the way in which care is organised, the choice of standard treatment, differences in care consumption, differences in costs and perspectives, etc. For more information about this, we refer the reader to the guidelines for health economic research that have currently been updated by the Zorginstituut.

4.4 Preconditions

The Zorginstituut feels it is important that guideline developers should continue to follow the path they have chosen in involving cost-effectiveness in their guidelines. We see a number of points for attention that could assist them in this:

- More collaboration could be realised between guideline developers and ZonMw in respect of collecting data on the cost-effectiveness of interventions that are discussed in guidelines. One possibility could be to give priority, within the ZonMW's cost-effectiveness programme, to the guideline development agenda.
- Financial support should be realised for carrying out health-economic research. Involving the standard of cost-effectiveness in guideline development takes precedence over medical content. Because of the societal importance of this taking place, we feel it would be unrealistic to expect the professional group to bear these costs alone. We therefore argue that health insurers and the government should provide a structural financial contribution.
- Making a major investment in involving cost-effectiveness in drawing up guidelines is of crucial importance. Furthermore, constant attention will also have to be given to implementing these guidelines and to compliance with them.
- Lastly, it is important that we continue to realise that collecting cost-effectiveness data is not a goal in itself, but a means to be able to make better choices in health care. The means must always remain in proportion to this goal. In practice, therefore, we will have to learn for which (type of) guidelines this is

and is not useful.

5 Conclusions

Society finds the use of cost-effectiveness in health care controversial. This is largely due to the idea of people with severe disorders being deprived of their chance of a longer life or a better quality of life, purely because treatment is said to be too expensive. Frequent examples of this can be seen in the media, and it has resulted in a so-called contrast between 'identifiable victims' and 'statistical victims'. This means that we find it easier to empathise with a single recognisable victim than with enormous numbers of unrecognisable victims, despite the fact that the latter may be confronted with a massive amount of human suffering²⁸.

Nevertheless, there is a growing realisation that continued growth in health care costs and increasingly expensive innovative forms of care are becoming a problem. Not only because there is ultimately a limit to the money that we feel willing to pay for health care, but also because it raises the question of whether that money is being spent optimally. In short: whether we are disposing of our collective resources responsibly.

Cost-effectiveness is one criterion that helps us to make responsible choices. It gives us insight into how much "value we are getting" for our money. And whether in some cases it may be better to make a different choice. This is based on the fact that, as a population, we want to get the maximum in health gains for the premiums we pay. And that we do not want the resources to go to patients who could have taken care of their own interests. Naturally, it is also important to bear in mind situations in which exceptions should be made, for instance when people suffer a life-threatening disease for which no alternative treatment exists. The important thing is that our decisions are well-informed and that they are made transparently.

The minister put several questions to us that we have dealt with in this report. In summary, our replies are:

- *Elaborate upon the cost-effectiveness criterion.*

This report shows how we have operationalised the cost-effectiveness criterion. Relating the combination of data on burden of disease and costs per QALY to various classes of reference values results in a picture of whether the cost-effectiveness is favourable or unfavourable. In addition to cost-effectiveness we assess whether there are arguments that could make us want to accept higher or lower costs per QALY, and we determine the hierarchy in these arguments. Based on weighing up all relevant arguments, we arrive at advice on whether or not to reimburse. That advice may involve weighing up whether it is desirable and useful to improve an unfavourable cost-effectiveness by using one or more instruments.

The Zorginstituut will use this working method not only for medicines, as currently often takes place, but also for assessments of outcome. We will also constantly weigh up whether this is cost-effective, with the help of criteria for a risk-based assessment.

- *Can we adopt the working method of NICE regarding the use of cost-effectiveness data in reimbursement decisions?*

²⁸ Article Job Kievit "What do we care?"

Many of the countries surrounding us make use of cost-effectiveness data, whether or not as we use them in the Netherlands. Often it is not exactly clear how they do this. It is explicit, however, in the case of NICE, which uses cut-off values for cost-effectiveness in its appraisals. In principle, an intervention will not be reimbursed above these cut-off values. However, this working method has received a lot of criticism in recent years and NICE is also involving other arguments in their assessments (e.g. in the so-called "end of life"-discussion and in assessing expensive medicines against cancer).

The working methods of NICE, which are often regarded as exemplary, cannot be adopted as they are because of a number of contextual differences. Nevertheless, the system in the UK does have strong points from which we can learn, such as the transparency of the process and involving stakeholders in decision-making.

- *Compile possible scenarios for a statutory anchoring of the cost-effectiveness criterion.*

In order to emphasise the importance and the weight of the package criteria in our advisory capacity, and to confirm its societal and political basis of support, we feel it is desirable to anchor the fact that the package criteria should serve as a basis for our advice to the Minister about the composition of the basic package. Involving the package criteria in our advice on the composition of the package would give it a more compelling nature. We recommend that the regulation is not limited. After all, this would preclude in advance, and by definition, that the Zorginstituut could also involve other considerations in its advice. And that would actually render the working method described in this report impossible.

The Zorginstituut has brought the discussion about cost-effectiveness a step further by elaborating on the cost-effectiveness criterion and by indicating how we will use this criterion in our societal deliberations. An assessment of the package criteria according to this working method will contribute to a transparent and meticulous assessment and thus also to responsible decisions about insured care, which society will perceive as meticulous, comprehensible, reasonable and fair.

Zorginstituut Nederland

Chair of the Executive Board

Arnold Moerkamp