Methods
for Assessment of the Relation of Benefits
to Costs in the German Statutory
Health Care System

Version 1.1

09.10.2008

Contact:

Institute for Quality and Efficiency in Health Care (IQWiG)

Dillenburger Straße 27

D-51105 Cologne

Tel.:   +49 (0)221 / 35685-0

Fax: +49 (0)221 / 35685-1

E-mail: knb-methoden@iqwig.de

This Report on the proposed Methods is the result of a process of consultation with an International Expert. The lead author, Jaime Caro, is the chair of the Panel and the other experts on the Panel have reviewed all versions and provided extensive comments, some of which expressed disagreements with some of the methodological details. Throughout the process of developing the Methods, there has also been extensive consultation with IQWiG to ensure that the German context is well understood and IQWiG's needs were met.

The panel consists of eight international experts in health technology assessment, representing countries with strong backgrounds in this area (e.g., Australia, United Kingdom, Canada).

Members of the IQWiG International Expert Panel

Vincenzo Atella	University "Tor Vergata", Rome	Italy
Jaime Caro, Chair	Caro Research Institute, Concord	USA / Canada
Gérard de Pouvourville	ESSEC Business School, Cergy	France
David Henry	University of Newcastle/ ICES	Australia
Maurice McGregor	McGill University, Montreal	Canada
Alistair McGuire	London School of Economics	United Kingdom
Erik Nord	Norwegian Institute of Public Health, Oslo	Norway
Uwe Siebert	UMIT, Hall in Tirol	Austria

This is the operational version of the Methods for Assessment of the Relation of Benefits to Costs in the German Statutory Health Care System, published after broad consultation with experts and stakeholders. Further discussion of these Methods is explicitly desired in order to achieve continuous improvement.

Additional technical documents cover details of the cost estimation, modelling and uncertainty.

The technical document "Modelling" was written under guidance of Prof. Caro and Prof. Siebert, the technical document "Uncertainty" under guidance of Prof. Atella and the technical document "Cost Estimation" under guidance of PD Dr. Krauth (Hannover Medical School, Institute for Epidemiology, Public Medicine and Healthcare Systems Research).

Preamble

With the introduction of the health care reform in 2004 (Health Care Modernization Act; *Gesundheits-Modernisierungsgesetz, GMG*), legislation determined the establishment of an independent scientific Institute, within the German health care system. In June 2004, the G-BA *(Gemeinsamer Bundesausschuss, G-BA)* set up this scientific institution in the form of a non-profit and non-government private law foundation that has legal capacity. The sole purpose of the foundation is the creation and maintenance of the Institute for Quality and Efficiency in Health Care *(Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG)*.

The foundation's bodies include a Foundation Board and a five-member Board of Directors. The Institute is an establishment of the foundation and is under independent scientific management. The Institute's advisory committees are a 30-member Board of Trustees and a Scientific Advisory Board. The Scientific Advisory Board is appointed by the Board of Directors, and comprises 6 to 12 members. The Institute's Steering Committee includes the Institute's Management and the Department Heads. A Methods Group, which includes members of the Steering Committee, produces and modifies the Methods paper and develops and modifies the Institute's working procedures. The seat of the Institute is in Cologne.

As part of the Institute's responsibility to support the G-BA in fulfilling its legal duties, it submits evaluations concerning the benefits and harms, as well as of the economic implications, to contribute to continuous improvement in the quality and efficiency of health care for the German public. The G-BA has asked that the assessment of the benefits and costs be performed by comparing a health technology with other health technologies in a particular therapeutic area, taking into account the additional costs in relation to the additional therapeutic benefit. The Institute's aim is to develop the independent scientific capacity to answer the research questions posed, to evaluate medical issues and concepts relevant to health care, and to investigate research requirements relevant to patients' needs. The information compiled is relayed to the Federal Ministry of Health, the G-BA, and the public. The Institute fulfils its duties by producing reports on specific topics requested by the G-BA or the Federal Ministry of Health. It also initiates, coordinates, and publishes scientific work in areas where health care knowledge needs to be complemented.

This document has been produced according to a set of key conditions that define the legal requirements as well as the scientific context in which methods for the economic evaluation of health technologies for IQWiG must be developed. Although there is some room for interpretation, the legal requirements for assessments of the relation of costs and benefits of health technologies are embedded in the German legislation according to § 35b SGB V (Social Code Book V) [1]. IQWiG's mandate to the Expert Panel imposes some additional constraints, which the Expert Panel has been asked to adhere to in the production of these recommendations for the Methods. In doing so, the Panel has refrained from making some recommendations — particularly in terms of methods that have to do with priority-setting across the health care system — that might otherwise have provided for information that can be useful for decision-makers. If any of these requirements change, then it is possible that the Methods will need to be revised accordingly.

In comparison to other health care systems, in the EU and elsewhere, fixed expenditures limits have not been set at a national level in the German system. Additionally, there is the principle that citizens not be deprived of beneficial health technologies on cost grounds alone. In consequence this has meant that effective therapies are adopted initially regardless of the price. With recognition that this approach will not be sustainable, however, IQWiG has now been charged with developing the analytic framework for economic evaluations of drugs and other interventions.

In part because Germany has not operated its health care system within a fixed national budget, the basis for economic evaluation in Germany is not the same as in other systems: it does not involve establishing funding priorities across the health care system nor are the associated trade-offs in resource use and effectiveness taken into consideration. Instead, the legal framework, as understood by IQWiG, envisions a narrower goal of addressing the ceiling price at which a superior health technology *in a given therapeutic area* should continue to be reimbursed. This ceiling price represents the maximum that the GKV-Spitzenverband (the national umbrella organization for the statutory health insurance funds) considers should be paid for the benefits produced. This judgement is informed by IQWiG's evaluation; first, to establish that an additional benefit exists in comparison to existing treatments, and then when commissioned, to address the balance of costs and benefits. For example, when assessing a new effective treatment for Diabetes mellitus, IQWiG would have

assessed what the increased benefits are compared to the best existing hypoglycemic agents and then estimated its impact on costs. This information, with reference to the benefits and costs of antidiabetic agents on the market in Germany, is provided to the GKV-Spitzenverband for aid in setting the ceiling price. Any additional expenditure, however, does not need to be weighed in terms of what it could achieve in other therapeutic areas, much less in other areas of the economy, such as transportation, education or agriculture.

The explicit focus in each evaluation on a single therapeutic area is specific to Germany. It is much more common in health technology assessments to attempt to address the question of allocation of resources across the entire health care system. This is why a common measure of value[1] is sought, although even in other jurisdictions the comparisons are also done within a single therapeutic area. These comparisons across areas inevitably involve judgements about the societal value of treating one disease versus another and of the value of the health benefits of one intervention in comparison to those of other interventions (even if they are implicit only). No universally accepted method for doing this has yet been found. Instead, the IQWIG method takes a rather pragmatic approach aimed at comparing the efficiency of newer treatments in a therapeutic area with the efficiency of existing treatments. It specifically does not address the broader issue of prioritizing across the health care system. Thus, the evaluation aims to inform the decision-maker concerning the efficiency of a given technology compared to existing technologies in that therapeutic area, but it does not attempt to judge whether a particular condition deserves treatment relative to others or how much should be spent on it. This application of citizens' values is left to the decision-making bodies designated by law.

The economic evaluation is carried out to assist the GKV-Spitzenverband when it considers the appropriate ceiling price for reimbursement on behalf of the community of insured citizens. Thus, the assessments must be undertaken primarily from the perspective of the community of citizens insured by Statutory Health Insurance (SHI). This implies that only the costs which they bear - either by fees for the SHI or directly - should be included, but also means that some costs which might sometimes be excluded from evaluations could be incorporated in this case. Thus, if the diabetic agent reduces patient expenditure per patient,

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[1] For example, the Quality-Adjusted Life Year (QALY)

for example, this can offset any increase in the cost of the agent itself. More important, perhaps, is that this requirement also determines the point of view for judging whether any additional expenditures are reasonable: that of citizens insured by the SHI.

The law specifies that estimation of the benefit has to be conducted according to the standards of evidence-based medicine (EBM) while the economic evaluation must be in accord with the relevant internationally recognized standards, particularly in health economics. As there is no single set of economic evaluation standards recognized today, the Methods have been produced with a view to being consistent with generally accepted principles of health technology assessment.

Another major constraint is that the economic evaluations will only address those health technologies that have been judged to be superior (presumably to existing ones) and that the health benefits to be considered in the economic assessment are those which have been assessed by IQWiG following its published Methods grounded in the principles of EBM. This has several implications. It means that new inferior therapies will not be evaluated economically, even if they are considerably less expensive than existing ones. It also means that the effectiveness component must reflect the review carried out by IQWiG beforehand - no additional benefits, even if indirectly implied by the EBM measures, are to be included.

Economic evaluations must allow for appropriate transferability of results to the German health care system, and must consider local conditions relating to epidemiology, health care resource availability, access to health provision, clinical practice, reimbursement of service providers, and organizational structures.

IQWiG defines project-specific methods and criteria for preparing assessments of drug and non-drug health technologies. Not all steps in an evaluation process can be presented in advance and in detail in every case. Individual procedures are, amongst other things, dependent on the particular research question, the scientific evidence available, and any comments received. This document suggests a process by which the efficiency of a contemplated technology can be compared with the efficiency of existing technologies in the same therapeutic area. The evaluation procedure referring to each commission is developed and presented in the particular Protocol (*Berichtsplan*) and "Preliminary report" (*Vorbericht*).

The basis for comparative health economic evaluations presented here meets the requirements imposed by the German context while remaining as consistent as possible with existing scientific standards in the field [2].

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Summary

Background

In this report, the proposed method for use by IQWiG for economic evaluations is described. The evaluations to be conducted by IQWiG are intended to address the reasonableness of the price of introduced medical technologies and to provide information to the GKV-Spitzenverband for setting a ceiling price for these technologies. The evaluations take place after approval of the intervention (i.e., *ex post*).

It is important to stress that it was not in the mandate of the Panel to recommend methods for setting reimbursement priorities across the health care system; that is, for comparing the value for money of a new intervention with that obtained in health care in general (i.e. in other disease areas). The challenge given to the Panel was to describe how information that may serve as guidance to decision makers regarding ceiling prices can be extracted from the existing state of affairs within a given therapeutic area.

It is possible to extract such information, although the degree of guidance will depend on the particular circumstances of a given therapeutic area.

The Method

The main features of the proposed method are:

1. For each existing intervention, the net total disease-related cost per patient (including insured costs and those borne by patients or other payers) is estimated using scientifically sound methods, including modelling, appropriate to the German context. Requirements of cost calculations are described in chapter 4 of this report and detailed in a separate technical document.

2. The health effects (known as "benefits" in the German context) of each intervention, previously estimated by IQWiG, are transferred to the economic evaluation.

3. The valuation of the full health effects requires determining their *value* to the insured citizens. There are several key considerations in doing so:

   a. Considering the prognostic implications within a health economic evaluation modelling could be necessary.

b. For the efficiency estimates to be meaningful, the value of benefits must be measured on a cardinal scale (or approximately so).

c. An intervention's value may be proportional to its medical effect, in which case the latter may be plotted directly as a correlate of value.

d. This is not always the case, however. A reduction in pain of 2 units — say from 4 to 2 on a pain scale of 1 to 10 — is not necessarily twice as valuable as a reduction of 1 unit at a different place in the scale, say from 7 to 6.

e. Standard generic utility instruments like the EQ-5D can be helpful in judging the value of multi-dimensional effects. So can data from studies of quality of life of patients (so called "experience utility").

f. The multiplication of quality by the duration of that quality to obtain "well-year equivalents gained" can also be helpful, but only to the extent that the resulting "QALYs" are a cardinal correlate of value.

4. To present the information clearly yet comprehensively, an "efficiency frontier" plot is created. Each intervention is plotted on a coordinate system with the net total costs per patient on the horizontal axis and the value of health benefits (and harms) on the vertical axis:
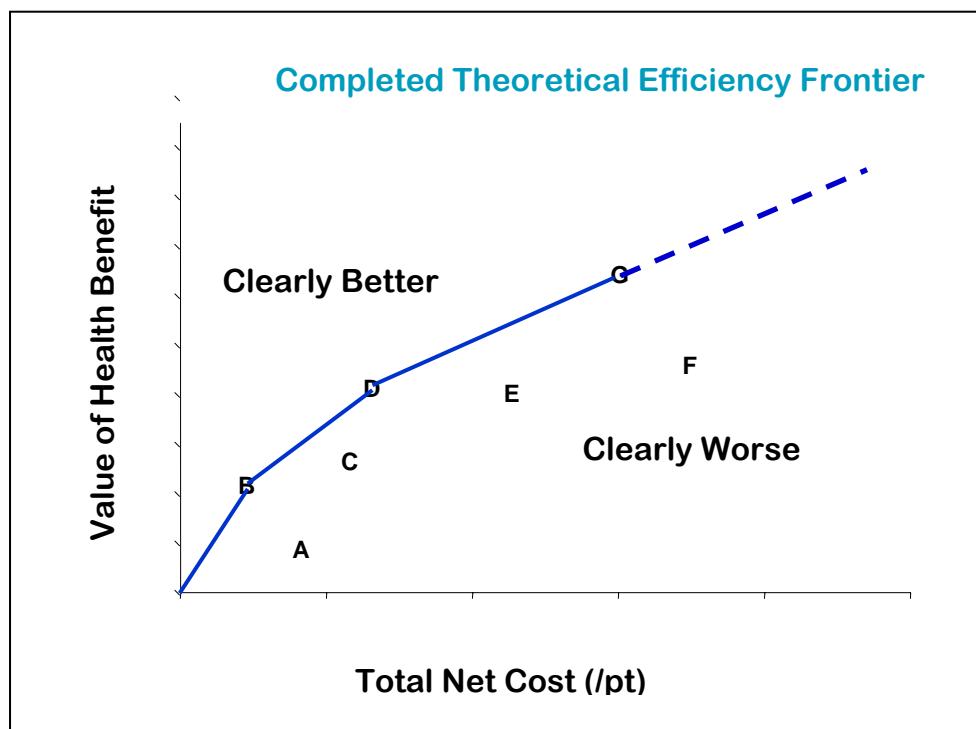
Figure S-1 Completed theoretical Efficiency Frontier

    a. The resulting plot gives decision makers a broad picture of how much value is being obtained for the resources presently deployed in the area in question. At a glance, the decision maker gets an impression of both the "going rate" of value for money and the degree of variation across treatment options.

        i. The efficiency of any new intervention at issue may be assessed in light of those on the plot.

        ii. If it is clearly better (i.e., above and to the left of the efficient "going range"), then it suggests that its current price is reasonable (more efficient than current practice).

        iii. If it is clearly worse (i.e., below and to the right of the efficient "going range"), then it suggests that its current price is not reasonable and should be adjusted down to a reasonable ceiling price.

iv. If it is in the same value-to-cost range as efficient existing interventions, then its current price may be reasonable, but this requires further judgement. This is particularly true of interventions at issue that are both superior and more costly than existing ones – which is often the case.

5. Some help lines indicated by the "going range" may be plotted.

   a. One is the line from the origin to the existing intervention providing the current "best" value in health benefits.

   b. Another could be the line showing average value-to-cost ratios of existing interventions (mean value-for-money in the area in question).

   c. There is a theoretically grounded line, however: the upper boundary of the plot of interventions. This theoretical efficiency frontier connects a subset of "most efficient interventions" in the area. They are most efficient in the sense that none of them are dominated by other interventions - neither absolutely (i.e., there is no other intervention that is both less costly and more valuable), nor in extended fashion (i.e., there is no pair of interventions whose weighted average will yield more value at less cost).

6. The slope of the efficiency frontier decreases from left to right. This follows from the way the frontier is constructed. However, in a therapeutic area with a fair number of competing options (enough observations to show a trend), the decreasing slope may also be seen as reflecting the law of diminishing marginal returns, i.e., the fact that even in the subset of "most efficient therapies", increases in costs of R&D and production provide less and less additional value. In this case, the frontier provides information on the rate of this decline in marginal returns.

   a. This estimate of the rate of decline indicates "what is to be expected" in terms of cost increases for new interventions that provide more value than earlier ones.

   b. Decision makers may choose to use this as guidance by considering the position of the newer intervention in relation to the expectation.

    i. If the newer intervention lies on or above the expectation, it is in a sense performing better than one could expect and there is thus no indication that there ought to be a lower ceiling price.

    ii. If the newer intervention lies below the expectation, then there is indication that at the product's level of value the ceiling price should be set consistent with the tendency of the efficiency frontier. Higher prices would require additional rationale.

It is important to stress that the fewer competing interventions, the less ground for interpreting the frontier in this way.

7. The "going rate" reflected by existing prices and benefits does not necessarily correspond to insured citizens' willingness to pay for those benefits (given that in most cases, citizens will not have been asked). External willingness-to-pay values can be incorporate in the plot. These would then provide additional guidance to decision makers.

8. The efficiency frontier plot may be used for other purposes as well.

    a. If the price of the last (previously best and most expensive) intervention on the frontier was set based on an economic evaluation in comparison with the other interventions in the therapeutic area (or at least with the second best therapy on the frontier), then the last line segment of the frontier indicates the marginal willingness to pay for increased value in that therapeutic area. A new intervention that yields an equal or better incremental value-to-cost ratio than this (relative to the previously best therapy) may *a priori* be said to be consistent with prior willingness to pay. Still, decision makers need to consider whether previous willingness to pay continues to apply as new technologies are developed.

    b. The diagram also shows clearly inefficient interventions (i.e., those that are both more costly and less valuable than other existing options). In principle, questions may be raised as to whether the prices of such options should come down.

c. For interventions that are not on the efficiency frontier but are not "absolutely" dominated, the guidance could be that their price seems too high and should be brought in line with the extended efficiency frontier or a justification for not doing so needs to be provided.

Conclusion

It is possible to extract guidance for ceiling prices in a given therapeutic area from information on the benefits and costs of existing therapies in that area. The strength of the guidance will depend on the number of existing therapies in the area. The Panel stresses that the proposed method should serve as a tool to inform deliberations on ceiling prices in Germany. It does not produce a decision rule.

<div align="center">SECTION 1</div>

1 Introduction

Every policy decision on resource use should be preceded by a comprehensive, scientific evaluation of the relevant facts regarding how valuable the health benefits are and the costs of obtaining them. Although these sound and consistent evaluations of all relevant aspects are essential prerequisites to inform policy decisions, they cannot replace the decision making process.

To ensure consistency and transparency, there must be a formal basis for economic evaluations. This formal basis provides the analytic framework that all assessments are to use for structuring the information and guiding the reimbursement decisions. Thus, it must be sufficiently general that it can handle all potential subjects of an evaluation and it must encompass all of the required elements in a clear, systematic way. The framework must also be feasible to implement with a reasonable investment in effort and time and it should fit well within the local context as specified by the law and regulations.

1.1 Process of Creating the Guidelines

With the coming into force of the "Act to promote competition of the statutory health insurance" on 1 April 2007, the assessment of the benefits and costs of drugs was introduced as a task for IQWiG. This assessment concerns primarily prescription drugs that have recently entered the health care system. It is also applicable for important existing drugs and other health technologies. To undergo economic evaluation, health technologies have to show an additional benefit compared to other health technologies already available or other therapeutic options in use in the health care system. IQWiG is responsible by law, after being commissioned by the G-BA, to assess the balance of benefits to costs of these health technologies. Within the framework of the law, IQWiG has to ensure that the assessment of the medical benefit of health technologies is conducted according to internationally recognized standards of evidence-based medicine. The economic evaluation has to be conducted according to the relevant internationally recognized standards, particularly in health economics.

1.1.1 Selection of Experts

In compliance with the requirements set by law, IQWiG established an international expert for the development of a detailed and valid methodology for assessing the balance of benefits and costs of health technologies. For the recruitment of members of the IQWiG International Expert Panel, it was considered that there should be Experts from:

- Other European countries with health care system structure similar to Germany, especially concerning in- and out-patient care (e.g., Austria, France and Italy).

- Countries with long-established tradition in developing guidelines for, and performing, health technology assessments (e.g., Australia, Canada, United Kingdom).

Additional experts were selected based on their experience and competence in carrying out economic evaluations.

1.1.2 Development of Draft Guidelines

An initial meeting was held on 9 July 2007 in Copenhagen, Denmark. At that meeting, IQWiG presented to the Experts the legal conditions of the IQWiG International Expert Panel's mandate to produce the Methods for Economic Evaluations for the German Statutory Health Care System. Thereafter, the IQWiG International Expert Panel was established and began deliberations.

The chair of the IQWiG International Expert Panel wrote a first draft of the proposed Methods and presented it to IQWiG in August 2007. This draft was provided to the Experts at the beginning of September. It was reviewed in detail by each member of the IQWiG International Expert Panel. Members provided written reviews to IQWiG which were then considered in the production of the second draft.

At the end of September, a review meeting took place at Wiesbaden, Germany, where substantive comments of the IQWiG International Expert Panel members regarding the draft version were discussed. Consensus was reached on key aspects of the Methods, though differences in opinion remain regarding the valuation of benefits and the extent to which the economic evaluation should engage in priority setting across the health care system. In addition, it was decided to split the draft into a document that would contain all the

recommendations of the IQWiG International Expert Panel and a set of technical documents that would provide background and methodological detail. These supplementary technical documents have been completed in the meantime.

The expert comments and recommendations were incorporated into version two of the draft Methods. The revised main document was provided to the Experts for review on 15 October 2007 and a final draft version of the Methods was sent to the IQWiG Scientific Advisory Board and to the IQWiG Methods Group on 22 October 2007 for initiation of their review process. A further version of the second draft was produced upon receipt of these reviews and additional written comments from the experts.

This version was presented to the Expert Panel at a meeting in Cologne in the beginning of December 2007. At this meeting, IQWiG Scientific Advisory Board also presented a number of suggestions for amendments. In the following month, further refinements were made on the basis of ongoing discussions within the Panel, consultations with IQWiG's Methods Group, and the results of both workshops concerning assessment of benefits and costs organized by the Federal Ministry of Health (BMG) in 2007 [3-5].

The first public version of the Methods for Assessment of the Relation of Benefits to Costs in the German Statutory Health Care System (Version 1.0) was published for comment in January 2008. By the time the comment period ended in March, written comments had been submitted by more than 40 organizations. These comments were carefully reviewed by the staff at IQWiG and English translations were provided to all members of the Expert Panel.

The Expert Panel met to discuss the substantive comments in April 2008. These were grouped into major themes and a separate document was prepared presenting the Expert Panel's observations in response to these remarks. Where appropriate, text has been added to the Methods.

1.2 Organization of Report

The proposed Methods for Assessment of the Relation of Benefits to Costs in the German Statutory Health Care System are described in this document. Additional technical documents cover details of the cost estimation, modelling and uncertainty. The technical document "Modelling" was written under guidance of Prof. Caro and Prof. Siebert, the technical document "Uncertainty" under guidance of Prof. Atella and the technical document "Cost Estimation" under guidance of PD Dr. Krauth (Hannover Medical School, Institute for Epidemiology, Public Medicine and Healthcare Systems Research).

This main document is divided into three sections beyond this Introduction. The Basis for Economic Evaluations describes the framework for the assessments and the guidance it provides to decision makers. In the section on Estimation of Costs, the recommendations for calculating this component of the evaluation are presented.

Finally, the section on Budget Impact Analysis provides the approach to estimating the economic consequences of reimbursing new health technologies.

SECTION 2

2 Basis for Economic Evaluation

2.1 Introduction

None of the existing methods for comparative health economic evaluations are universally accepted as a basis for ceiling price assessments. The conventional, main stream method for economic evaluation is cost-utility analysis (CUA), with the quality-adjusted life year (QALY) as the unit of measurement of benefits; an approach that has been endorsed by several consensus groups [6] including one that comprises many German health economists [2].

The methodology that prevails today involves estimation of the additional costs and health effects of an intervention of interest relative to one or more existing interventions in the same therapeutic area. The health effects are often converted to a single measure of benefit, the QALY, by adjusting expected survival by the average quality of that life on the assumption that this aggregate measure reflects the relevant societal values in a cardinal manner. The two measures of impact are combined into a single one by forming a ratio of the incremental cost to the incremental QALYs. This cost-utility ratio is provided to decision-makers with the idea that they will use it to judge whether the added benefits of the intervention warrant any increased costs.

The incremental cost-utility ratio does not, by itself, address the reasonableness of the price of the new intervention. This appraisal requires an external standard that reflects how much the society is willing to pay for one unit of value and appropriate methods for setting this threshold have not been defined.

While it is true that this QALY-based CUA has been prominent for many years in scientific articles and is an aid to actual resource allocation decisions in a few countries (e.g., the UK and Australia), concerns for solidarity, equity and fairness have stopped CUA from being accepted by decision makers and clinicians in many other countries, and the trend today is to ask how such distributive concerns may be given greater weight in economic evaluation [7]. Moreover, conventional QALYs measure only the size of outcomes rather than valuing the benefits.

Thus, a modified approach is required in Germany. The framework for comparative health economic evaluations detailed in these Methods was designed to meet all the requirements imposed by the German context while remaining consistent with the theory underlying the prevailing methods in the field. It does so by modifying a method that is well known and accepted - though having its own limitations and being infrequently used explicitly in medicine.

Economics deals with the **value** of resources used and of the outcomes produced. Given the use of money as the currency of value in the marketplace, the term *value* is often misunderstood as something that necessarily has to do with money. It does not. It has to do with "the regard that something is held to deserve, its importance or worth" [8]. IQWiG uses the term **benefit** to refer to the health outcomes obtained through a particular intervention. Although this can be somewhat confusing as in economics this term refers to the value of those outcomes, IQWiG's usage is retained here. For example, an operation may increase a patient's ability to walk by 500 meters; this is the benefit. The *value* of this benefit is a matter of how highly it is appreciated by the recipient and others.

Economic evaluation is about comparing the value of the benefits with the cost of producing them. The cost expresses how much alternative value is sacrificed when money is spent on a given product or service. If intervention A costs twice as much as intervention B, then twice as much alternative value is sacrificed when someone buys A rather than B. To justify this choice to the purchaser, A should produce at least twice as much value as B. To be able to judge whether this is the case, the measure of value needs to be at a cardinal level, i.e., such that it is *meaningful* to say that A produces not only *more* value than B (i.e., ordinal level of measurement), but rather *X times more* value. Even if *X* will rarely be more than an *approximate* number (i.e., a rough judgement), it gives considerable more information than the purely ordinal judgement. This comparison of the value produced with the cost of doing so is the essence of the proposed Method.

2.2 Efficiency Frontier

Recommendation:

An efficiency frontier should be constructed for each therapeutic area as the basis for economic evaluation of relevant health technologies.

2.2.1 Rationale

The rationale for using the efficiency frontier is the same as when the focus is on incremental cost-utility ratios: efficiency is an important consideration for decision makers. It is, thus, useful for decision makers if efficiency and its components are explicitly computed and displayed. The efficiency frontier plot indicates how much value is being obtained at what costs and where existing interventions within a given therapeutic area are positioned relative to each other at that moment in Germany. This concept was chosen as the framework for IQWiG's assessment of health technologies because it meets the requirements imposed by German law while remaining consistent with the theory underlying approaches prevailing internationally. Specifically, the method allows consideration of the efficiency of resource use in a single therapeutic area, with retention of the benefits as established by IQWiG and avoidance of discrimination.

The proposed approach is founded on the same essential idea as the approaches that are common today. It differs from the common applications in several respects. First, it stipulates that the efficiency frontier be made explicit. This information, in and of itself, is expected to be useful to all stakeholders in the health care system. Second, rather than employ a universal threshold, the Methods propose to use the efficiency frontier itself to determine what is the prevailing lowest efficiency on the frontier in a given therapeutic area in the German market. Third, it does not seek to apply a single threshold across all interventions in the health care system. Such a determination of societal priorities is left to the body politic.

There is no need, or justification, for implementing cost-utility analysis, or QALYs in particular. The mandate for these Methods did not call for such a focus as the actual mandate was to examine whether one may extract information from the existing state of affairs within a given therapeutic area that may serve as guidance to decision makers regarding ceiling prices. With the efficiency frontier it is possible to extract such information, consistent with basic economic principles.

2.2.2   Definition

The efficiency frontier plot is a graph of the value of health effects provided by available interventions in a given therapeutic area against the net costs of providing these. The efficiency frontier connects interventions on that plot such that none of the points on the segment indicates better or worse efficiency than any other point on the frontier.[2] In other words, they denote the net cost at any given value that is consistent with the efficiency of the current market. Prices that place an intervention below the efficiency frontier indicate a lower efficiency and thus require additional justification. Prices above the efficiency frontier indicate improved efficiency and thus redefine the frontier (Figure 2-1).
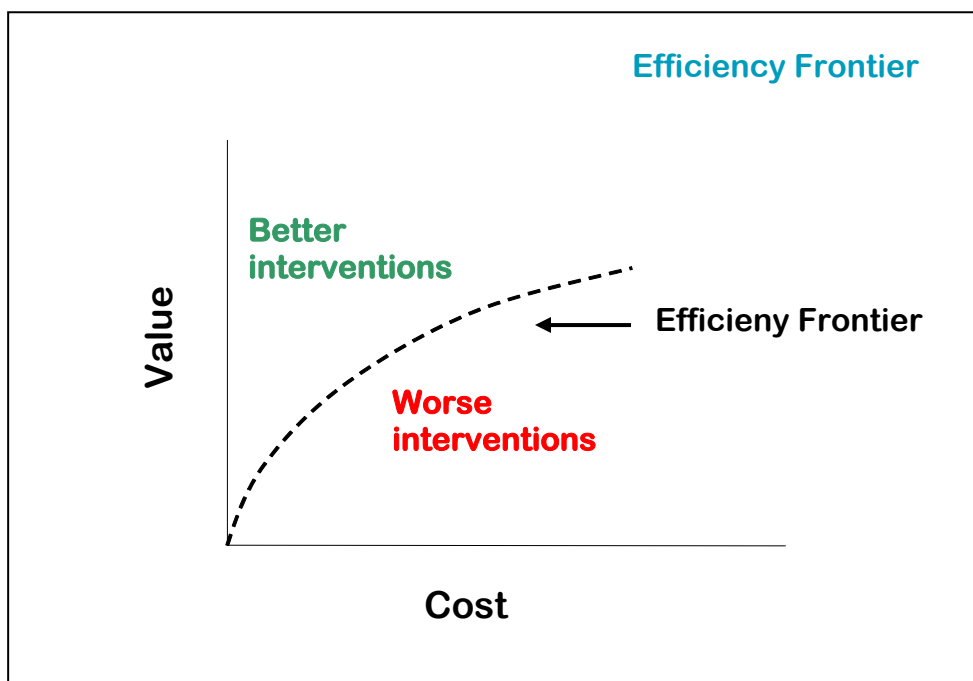
Figure 2-1 Basic concept of the efficiency frontier. It compares the value produced with the cost of doing so. Above the frontier is a zone of new interventions that are better than the existing ones in that particular therapeutic class because they produce more value for a given cost; while less efficient ones lie below it.

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[2] The precise definition and interpretation of the efficiency frontier requires some additional detail – see next section and section 2.4.

2.2.3   Concept

The efficiency frontier renders explicit the trade-off between an outlay - not necessarily monetary - and a consequent gain; and helps identify the options that provide a necessary condition for optimal return given any level of outlay. Its construction is best understood graphically (Figure 2-2). The elements of the evaluation — the outlay and the gain — are plotted on a Cartesian coordinate system with one axis reflecting the outlay and the other what is to be gained. The options are then plotted at their estimated levels and line segments are drawn through selected options to form the upper boundary (see precise description below). This line is the theoretical efficiency frontier.
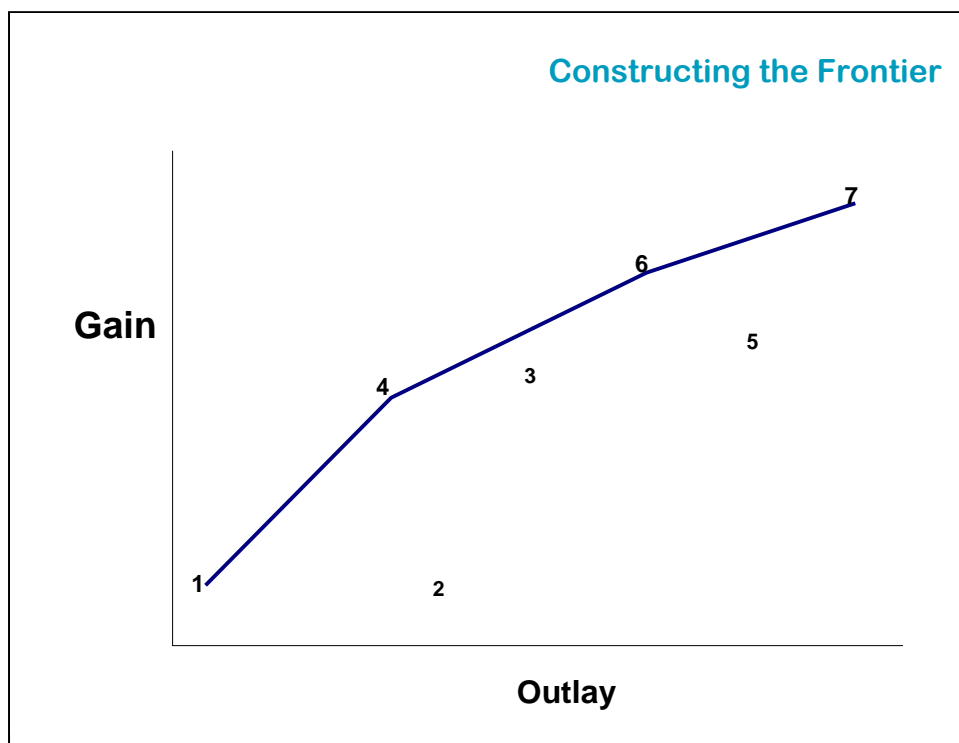
Figure 2-2 Construction of the theoretical efficiency frontier by plotting the seven available health technologies according to their required outlays and the gains they provide. The line segments identifying the health technologies with the highest gains for successively higher outlays form the theoretical efficiency frontier.

It is not of major importance which axis is used to plot outlay and which one for gain but there are some advantages to using the horizontal axis for the former and the vertical one for the latter. Not only does this accord with the most frequently-used format in other fields but it also provides for an easy graphical interpretation of the plots. The theoretical efficiency

frontier in a plot constructed this way reveals the next most efficient option going from left to right. The slope of the line segment connecting any two options gives the rate of gain per unit of additional outlay should a decision be made to shift patients from one therapy to the other. Thus, a horizontal segment (with slope zero) indicates that the option to the right adds cost with no discernible gain (i.e., zero efficiency) while a vertical segment (with infinite slope) indicates that the choice above provides gains at no additional cost (i.e., infinite efficiency). Choices that plot in between (with positive slopes) provide additional gains for additional outlays while those that plot below the horizontal (with negative slopes) reduce the gains while increasing outlays (i.e., negative efficiency) (Figure 2-3).
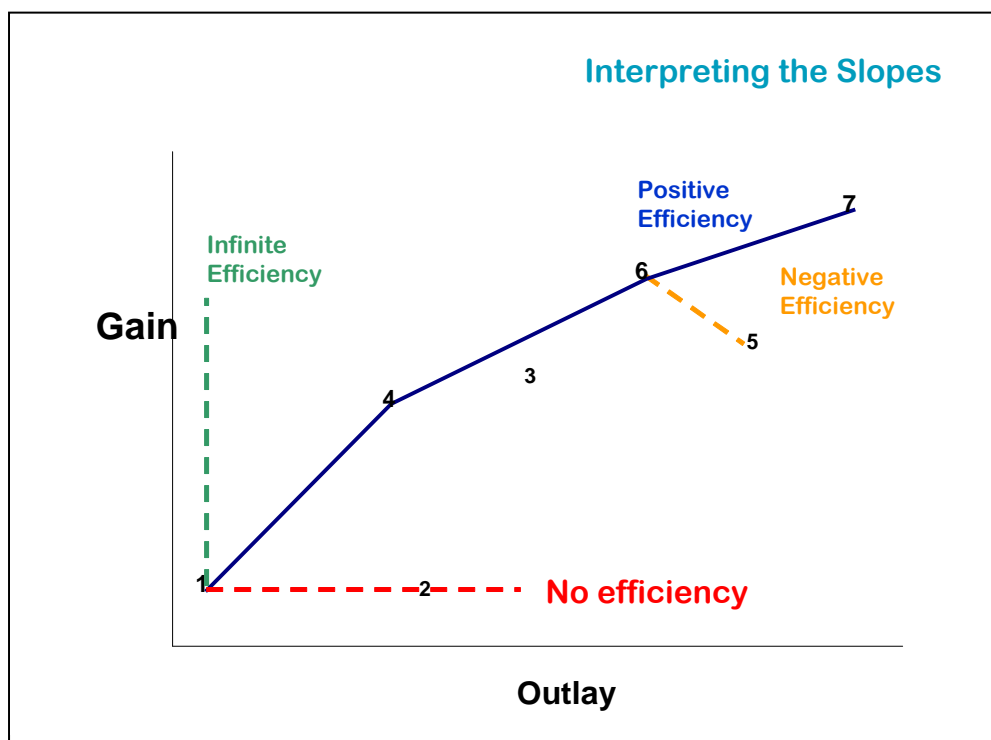
Figure 2-3 Interpreting the slopes given by the theoretical efficiency frontier. The horizontal slope indicates no efficiency (e.g., 2 versus 1) while the vertical slope indicates infinite efficiency. Positive slopes (e.g., between points 6 and 7) reflect additional gains for increased cost while negative slopes (e.g., between points 6 and 5) indicate less gain yet more cost.

The positions of interventions like 3 in Figure 2-3 require further interpretation as they do not reflect negative efficiency with respect to any existing intervention. In Figure 2-4, the area below the theoretical efficiency frontier is further divided by a series of rectangles (A-D), each one reflecting all potential interventions which would reflect negative efficiency (higher outlay with lower gain) with respect to at least one existing intervention on the theoretical

efficiency frontier. Options in these areas (e.g., 2, 5 in Figure 2-4) are clearly inefficient. This leaves triangular areas such as E, F, and G, where options are not clearly inefficient. Traditionally, options plotting in these triangles are not considered part of the efficiency frontier because a combination of the two options forming the hypotenuse of the triangle will provide more gain for less outlay.
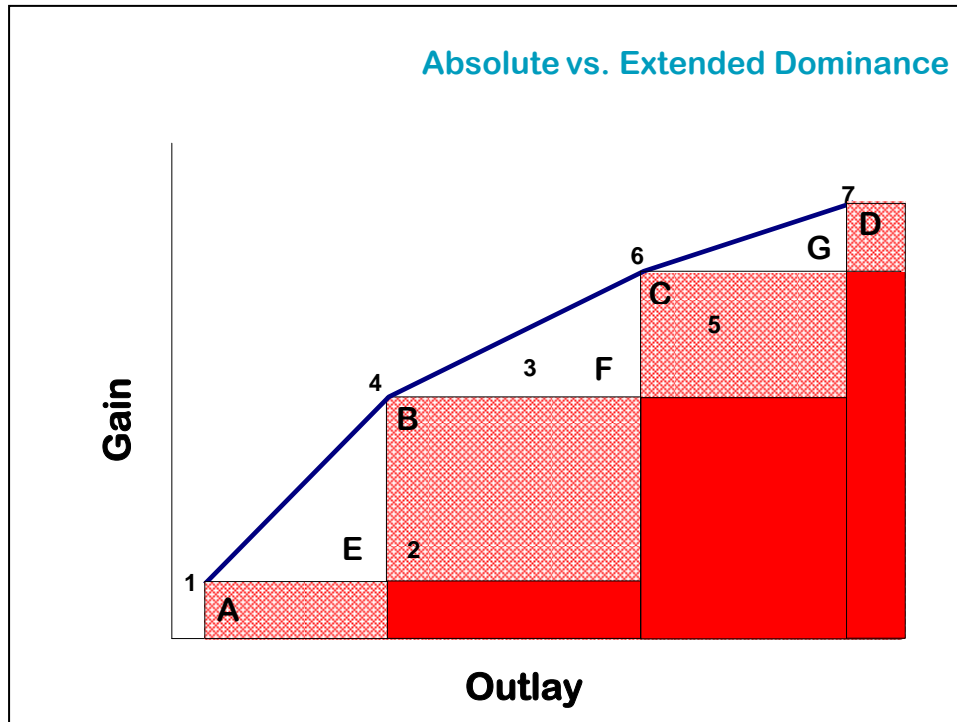
Figure 2-4 Absolute versus extended dominance. The theoretical efficiency frontier (solid line) joins those points that are not inefficient relative to any other option nor are combination of options. These options demarcate rectangles A-D and any options in those areas (e.g., 2, 5) are clearly inefficient. Option 3 is in one of the remaining triangular areas (E-G) where no single option is clearly more efficient – it is theoretically subject to extended dominance by a combination of 4 and 6 but this combined alternative may not be feasible in practice.

While such a combination may be possible, this is not always the case. It implies, for example, that if the price of option 3 is fixed, then its users would need to be redistributed to 4 and 6 to achieve greater efficacy. This may be undesirable clinically and may be difficult to justify, since it would lead to a loss for those who would get 4. The alternative of allowing users to alternate between the two therapies over time, is clearly not possible with most surgeries, and presumably not with many drugs either. Thus, there may be many situations where options in the triangles remain as part of the practical efficiency frontier. If extended dominance is not considered, then an absolute efficiency frontier is given by the "staircase" (Figure   2-5) that connects the tops of the dominating rectangles. A less strict frontier would result from simply allowing concavity of the theoretical efficiency frontier at point 3.
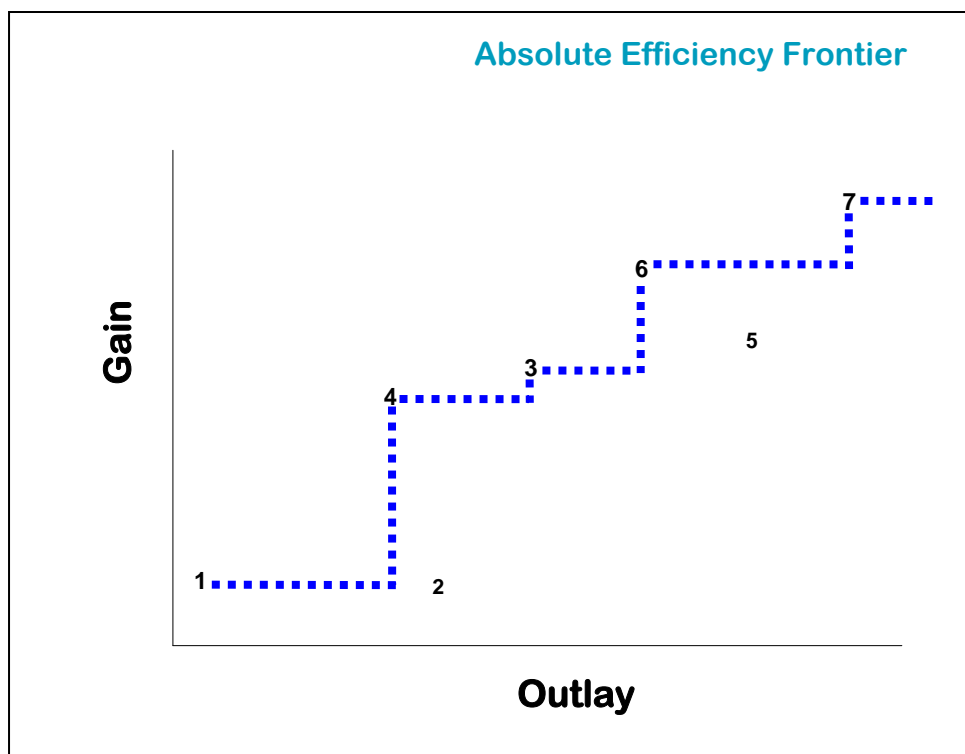

Figure 2-5 Absolute efficiency frontier given by the staircase incorporating an option (3) that is not clearly inefficient relative to the existing ones.

2.2.4 Key Modifications for Health Economic Assessments in Germany

In order to use the efficiency frontier as the basis for IQWiG economic assessments in Germany, the generic "gains" and "outlays" need to be defined specific to health care health technologies in the German context and the various decision-relevant zones must be demarcated and their corresponding guidance delineated.

Although there are some details to be specified (see section 3 below), the outlay in health economic assessments is, of course, the cost of the health technologies that are under evaluation. It reflects the net costs that are incurred if a given therapy is adopted and reimbursed at a particular price. This cost is plotted at its total net amount (considering any offsets from savings in resources that will no longer be consumed) rather than the incremental amount relative to the next less expensive intervention (Figure 2-6).
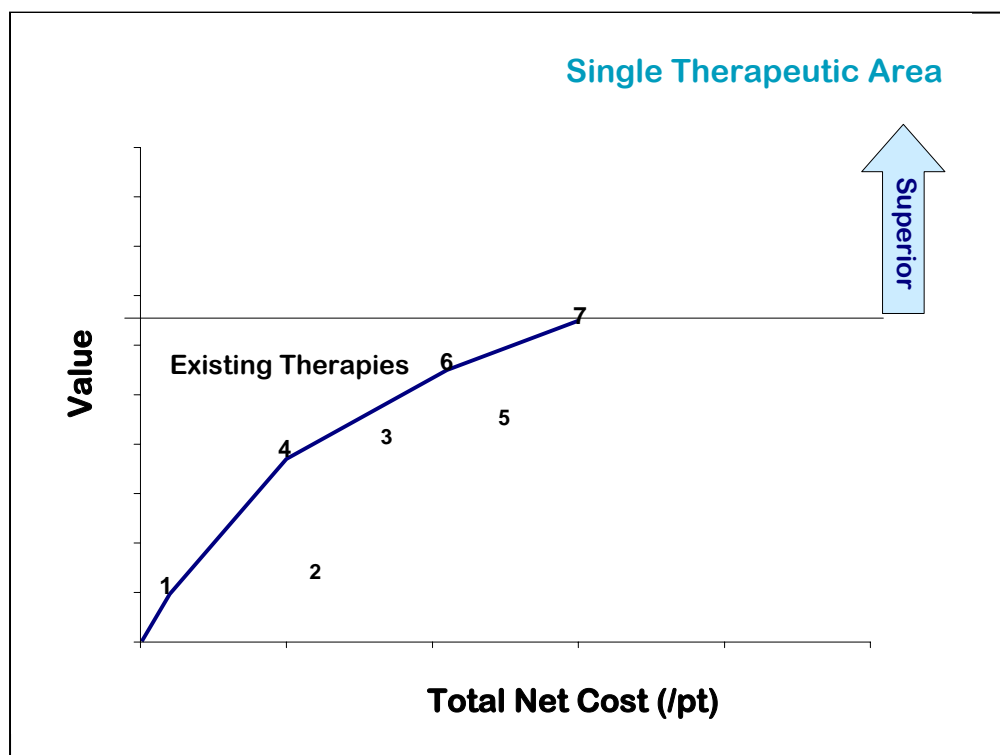
Figure 2-6 Theoretical efficiency frontier modified for use in Germany in the context of a single therapeutic area. The plotted numbers reflect the therapies that IQWiG has selected as appropriate comparators. (In reality, many of these therapies, especially 1 and 2, might not be evaluated because they are so inferior in terms of value but they are plotted here to illustrate the full graph).

The gain in a health technology assessment represents how valuable the improvement in health that a given intervention provides (above and beyond "doing nothing") is judged to be. In the German context, this must be based on the rigorous benefit assessment carried out by IQWiG before the economic evaluation. This imperative has substantial methodological implications for the economic evaluation (see Section 2.3.1). Among these are the parameterization of the benefit, the integration of a variety of health improvements and harms, how to address differential timings, and ensuring that the scale represents how valuable the benefit is in a cardinal manner. Additionally, there is the demand to avoid any discrimination.

2.3   Constructing the Frontier

Recommendation:

The efficiency frontier plot should be constructed so that it reflects the relevant health technologies in a given therapeutic area. This involves:

- **Full, detailed specification of the therapeutic area at issue. This may include the specific disease, the conditions of treatment (e.g., in hospital), the intended patient population, the therapeutic sequence (first, second, etc.) and whether it is mono- or combination therapy;**

- **Scoring existing therapies in terms of cost and how valuable the health improvement ("benefit") is;**

- **Locating therapies on a coordinate system with the value of the benefits on the vertical axis and costs on the horizontal[3];**

- **Drawing the efficiency frontier.**

Evaluation of new health technologies for the setting of ceiling prices in Germany is to be carried out in the context of the relevant efficiency frontier, that is, the one that captures the health effects and costs of the new and already available intervention in the intended therapeutic area.

In order to construct the frontier there are three major steps to take (Figure 2-7):

- Define the vertical axis, quantify the benefits for the chosen interventions and ensure the scale reflects how valuable these are judged to be in the therapeutic area of interest.

- Define the horizontal axis and quantify the total net costs per patient for each of the selected therapies.

- Plot the therapies and draw the efficiency frontier.

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[3] Tabular presentation is also possible, though the implications are not as obvious.

In this section, these steps are described in terms of the specific tasks required for the construction of the frontier. The Methods to be used in quantifying the benefits are described in IQWiG's publication [9], and the approach to quantifying the cost inputs in Section 3.
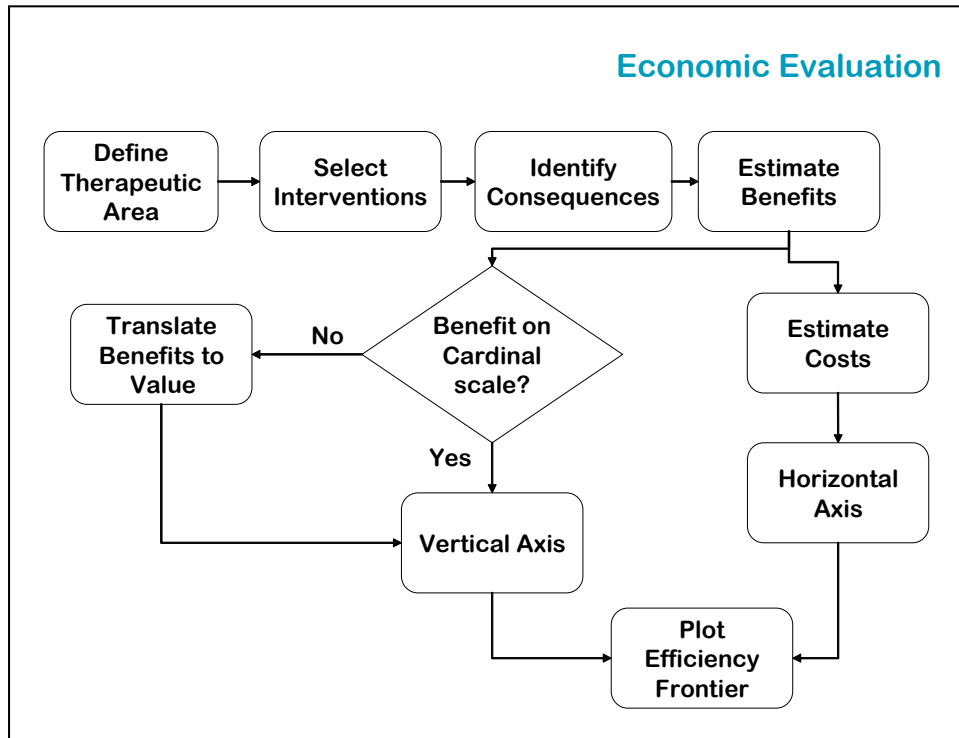

Figure 2-7 Proposed process of economic evaluation.

2.3.1 Vertical Axis

Recommendations:

- **The vertical axis should reflect the value of the health benefits assessed by IQWiG.**

- **The benefits should be parameterized in terms of patient-relevant benefits (which may include quality of life scores), or of the likelihood of benefiting, or of a score integrating the consequences.**

- **The benefit must be transferred to the vertical axis measured on a cardinal scale that reflects how valuable that benefit is. This transfer may involve modelling to address the (longer) time horizon required for economic analysis and capturing of the full value produced.**

To define the axis in a particular therapeutic context and be able to quantify the consequences for the selected set of therapies, it is necessary to:

- identify the clinical context for the health technology;

- specify the consequences to be considered, how to parameterize them and how to address multiple endpoints;

- select the health technologies to be assessed;

- estimate the specified consequences;

- establish the scale to be used to reflect how valuable the benefit is and translate the benefit to it if necessary.

The first four steps are already undertaken as part of IQWiG's benefit assessment and are thus not dealt with further in these Methods. They must take place, however, bearing in mind that they may be used for the economic assessment.

For example, the choice of health technologies to be assessed must reasonably reflect the existing marketplace in Germany at the time of the evaluation rather than being restricted to interventions for which there are head-to-head clinical trials.

The last step is specific to the economic evaluation. The main options are documented here.

Patient-relevant benefits of diagnostic and therapeutic interventions are identified in controlled clinical trials. In some cases valid models can predict how these benefits identified in clinical trials appear under other circumstances or time perspectives. However, under no circumstances can models generate new benefits.

2.3.1.1   Translating the Benefit for Economic Evaluation

IQWiG carries out the evaluation of benefit according to its published Methods [9]. IQWiG reaches one of five determinations for each predefined patient-relevant endpoint:

1) Proof of a(n) (additional) benefit or harm exists.

2) Indications of a(n) (additional) benefit or harm exists.

3) Proof of the lack of a(n) (additional) benefit or harm exists.

4) Indications of the lack of a(n) (additional) benefit or harm exists.

5) No proof and no indication of a(n) (additional) benefit or harm exist.

Determinations 1) and 3) require sufficient confident evidence of an effect or lack thereof; 2) and 4) imply that there is some suggestion of an effect or lack thereof, but the evidence for a proof is insufficient. In the absence of a clue because of insufficient data, IQWiG makes determination 5). For the economic evaluation, interventions for which evidence (or possibly indication) for achieving an additional therapeutic benefit is available in the sense of the above mentioned graduation would be included. In the sense of the above mentioned graduation only interventions for which evidence (or possibly indication) for achieving an additional therapeutic benefit is available would be included into the economic evaluation.

If IQWiG finds that evidence of an effect exists (i.e., comes to determination 1), the Institute presents the evidence basis for the benefit potential, and for the harm potential.

There is also the possibility of presenting a weighting of the benefits and harms. In this case, the determinations made by IQWiG separately for each patient-relevant endpoint would be reported by weighting the benefits and harms in a summarizing score. The weighting of benefits and harms would be topic-specific and should be set prospectively at the time the consequences to be studied are selected. This weighting, if carried out, would provide a solid basis for the economic evaluation that is consistent with the desired process in Germany.

Many commonly-used measures of benefit are not cardinal and thus are not appropriate measures of how valuable the benefit is. For example, on a ten-point functional scale of activities of daily living [10], a movement from level 8 to level 9 is not necessarily as valuable as one from level 4 to level 5. Similarly, for a person who is treated for a life-threatening illness, the prospect of gaining 20 years of life is not necessarily twice as valuable as the prospect of gaining 10.

In health economics, there are various procedures that purport to establish how valuable people think different improvements in health are at a cardinal level of measurement. The procedures include question techniques like the standard gamble, the time trade-off and the person trade-off [11], or the application of so called Multi Attribute Utility Instruments [12] like the Health Utilities Index [13,14] or health status scoring systems like the EQ-5D [15,16]. In principle, these procedures not only yield cardinal measures of how valuable the benefits are, but are also potentially helpful in producing summary measures when the effects of interventions are multidimensional (for instance, have several positive functional effects as well as some adverse effects).

In these Methods, no specific way of measuring value at a cardinal level is recommended because each therapeutic area may offer different possibilities for doing the assessments in a way that satisfies the cardinality requirement. Those who wish to use the proposed Methods are urged to bear in mind both the distinction between the *effect* ("*benefit*") and how *valuable* that effect is and the *cardinality* requirement for the latter. If these conceptual premises are not adhered to as far as possible in each therapeutic area that comes to examination, the proposed Methods will be less valid and useful. Although in practice it is not necessary to pursue perfect cardinal measures, it is important, however, to justify the measure chosen in these terms.

In order to translate the patient-relevant benefits to a cardinal scale that can be plotted on the vertical axis, it may be necessary to use modelling [17]. These patient-relevant benefits of diagnostic and therapeutic interventions are identified in controlled clinical trials. In some cases valid models can predict how these benefits identified in clinical trials appear under other circumstances or time perspectives. However, under no circumstances can models generate new benefits.

Thus, estimation of the intervention's implications for a patient's prognosis can be provided. These implications are important in assessing the value of that intervention - if they are not addressed then the economic evaluation will be flawed. Moreover, their absence will probably result in a time horizon that is discrepant with that for the costs.

2.3.1.1.1 Actual Clinical Measure

The actual clinical measures used by IQWiG are mortality, morbidity, health-related quality of life and validated surrogates. To be judged acceptable by IQWiG criteria, these surrogates must be supported by studies that have demonstrated convincingly that changes in these clinical measures translate to changes in patient-relevant outcomes. These surrogates are an option for the economic evaluation, provided that the translation is implemented via modelling.

The biggest advantage of these measures is that they have recognized clinical relevance, their measurement scale is familiar to clinicians and well established and most health technologies that need to be plotted on the efficiency frontier will have relevant evidence in this regard. Thus, it should be quite feasible to implement this for most well-studied therapeutic areas.

The main disadvantage to using a clinical measure is that it may not provide a cardinal scale that correlates well with the value of the benefit. In other words, changes in one part of the clinical scale may not have the same value as changes in another part. This may occur for several reasons — an important one being the existence of thresholds: a change that brings patients from an abnormal level into the normal range may be more important than the same change within the normal range. This problem with the benefit scale must be addressed case-by-case in the specific therapeutic areas. Clinicians and other experts must define the appropriate cardinal scale to be used in each therapeutic area.

If non-valid surrogates are used another problem would arise in that sense that evidence relating changes in the measure to changes in outcomes may be deficient. Thus, despite evidence relating the measure to eventual outcomes, (e.g., blood pressure to mortality) one may not know if the same relationship will exist when the measure is altered by therapeutic intervention. This problem is not specific to the economic evaluation but rather to the assessment of the benefits themselves. For that reason non-valid surrogates are not taken into account in both cases.

Another problem is that evidence relating changes in the measure to changes in outcomes may be deficient. Thus, despite evidence relating the measure to eventual outcomes, (e.g., blood pressure to mortality) one may not know if the same relationship will exist when the measure is altered by therapeutic intervention. This problem is not specific to the economic evaluation but rather to the assessment of the benefits themselves.

Moreover, a given clinical measure may only capture one aspect of the illness and be only partially related to other significant facets, if at all. Thus, a focus on microvascular complications in diabetes leaves out other morbidities which are important in the assessment and management of the diabetic patient, to say nothing of the side effects of treatments. This aspect will also need to be addressed case-by-case and may require development of specific instruments for a therapeutic area.

As the economic assessment is kept distinct from priority setting in Germany, there is no need for a universal measure of the value of the benefits; that is, for one that covers all possible health effects. The question remains, however, whether the QALY can serve as the summarizing measure of value within a therapeutic area. If tenable, this would be very useful, as substantial work has been done trying to provide general estimates of QALYs for many conditions. There are problems with the use of the QALY, even in the intra-therapeutic area, however.

One problem with the QALY involves the idea that quality and duration "trade evenly" so that an outcome of, say, 5 years at full quality may be seen as equivalent to one of 10 years at half quality. To many clinicians and policy makers this notion of equivalence between outcomes that are quite different in nature does not "feel right".

Another problem is that different techniques for valuing health states, and thus for estimating QALYs, yield different results. There is no international standard as to what is the preferred technique [7]. Thus, the QALY is not necessarily a good choice of summarizing measure in a given therapeutic area.

It is important for all stakeholders that the measures of value that will be used in each area are defined well in advance of any evaluation.

2.3.1.1.2 Use of a Responder Measure

Another approach for parameterizing the benefit is to estimate the likelihood that a patient will respond (i.e., achieve a specified net benefit) with each intervention. To do this, it is necessary to define what is meant by this *responder* concept, specific to each therapeutic area. Presumably, it involves achieving a particular threshold of benefit in one or more aspects of the condition without suffering side effects of such an extent that they cancel out those benefits [18]. Such *responder* definitions already exist for many illnesses and are even used as primary endpoints in clinical trials [19,20]. If none have been defined, or if they are not consistently used as the basis for evidence in a particular therapeutic area, then an important step in the evaluation would be the development of this definition [21]. If a responder measure is chosen as the benefit, then this should be undertaken as part of the benefit portion of IQWiG's assessment.

The obvious weakness of the responder measure is that it does not distinguish between responses of different magnitude. An argument in favour of the measure can be made, however, in that in some areas the most important step for patients is to obtain *some* significant improvement. This corresponds to a premise of so called "cost-value analysis" of health care [22], where society in valuing health programmes is assumed not to want to discriminate strongly between programmes for patients with different potentials for health – as long as the programmes yield significant effects.

The responder measure may be parameterized as the response rate or the likelihood that a patient would benefit. Should a responder concept be defined for a particular therapeutic area, its use in setting the vertical axis for plotting the efficiency frontier needs to be justified in detail and the drawbacks to its use fully elucidated.

2.3.1.2 Other Settings

2.3.1.2.1 Time Horizon

In many therapeutic areas, the benefits are measured by most clinical trials over much shorter periods than justified by the characteristics of the illness. While this may provide a feasible way to establish *whether* a benefit exists, proper quantification of that benefit and its translation to how valuable it is, requires that the prognostic implications of the short term effects be estimated over a time horizon that reasonably covers the extent of the illness. For many chronic illnesses, this amounts to the patient's remaining life time. Careful justification of the time horizon chosen and of the data sources used to estimate the prognosis must be part of the evaluation. In no case should prognosis setting lead to the "creation" of additional benefits that have not been documented in the EBM evaluation.

2.3.1.2.2 Discounting

When economic evaluations contemplate effects over time, they must see to it that they account for the impact of differential timing on how valuable those effects are judged to be. This discounting can take place according to the same methods used for costs (addressed in section 3.2.5.2 and more fully in the technical document) but it can also be argued that the differential timing can be incorporated directly in assessing how valuable the benefit is [23] . Either way, the approach must be fully justified.

2.3.2 Horizontal Axis

Recommendations:

- **Total net costs per patient should be plotted[4] on the horizontal axis.**

- **The costs should be estimated from the perspective of the community of German citizens insured by the SHI.**

- **The time horizon should be sufficient to cover the majority of relevant costs.[5]**

- **The costs should be the actual ones that are expected to accrue.**

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[4] It can also be tabulated.
[5] This may pose some difficulty if it is discrepant with the time horizon that was used for the benefit estimation. If this occurs then either the discrepancy must be carefully justified or it must be resolved.

The horizontal axis of the efficiency frontier reflects the economic consequences of the health technologies assessed. Several of the steps to defining the cost axis in a particular therapeutic context and being able to quantify the economic consequences for the selected set of therapies are identical to those for the vertical axis. Thus, it is necessary to:

- identify the therapeutic context and

- select the health technologies to be assessed.

These steps will have already taken place as part of the benefit assessment. There are some additional steps that are particular to the evaluation of costs:

- specify key settings that affect the costs,

- determine how to parameterize the economic consequences.

Beyond defining the cost axis, there is the actual estimation of costs. Those steps are detailed in Section 3.

There are several factors that have a major impact on the estimation of costs and these are detailed in Section 3. Two of them, however, have a specific influence on the horizontal axis of the efficiency frontier. These are the perspective taken and the time horizon.

2.3.2.1 Perspective

The perspective of an economic analysis refers to the point of view that is taken when considering the various elements. This is important for costs, especially when these are presented in aggregated form, because it determines what goes into the total. Depending on the perspective, some items may not be an expense, and thus should not be included in the estimates.

Given the regulations in Germany, the perspective must be that of the German citizens who belong to the SHI. Thus, the costs to be plotted on this axis could be taken to reflect those disease-related items covered by SHI and also those that are borne privately by insured patients and their families, or other insurers. It is emphasized that the recommended perspective is NOT that of the SHI but rather of the insured citizens.

Extension of the idea of a citizens' perspective to cover consequences to other aspects of the health care system (e.g., teaching and research), let alone to other sectors of the economy (e.g., transportation, energy, agriculture), although these may also be of importance to citizens, is not viewed as feasible. This full "societal" perspective - though grounded in economic theory - is impractical.

Implications of illness, or of its management, for the productivity of affected citizens may be an important component of an evaluation. For practical reasons, however, it is not suggested that such factors be incorporated in the calculation of the costs. Rather, aspects such as loss of productivity should be estimated and reported to the decision makers separately.

If there are any departures from the recommended perspective, these will need to be justified fully in terms of the distortions that would occur in the analysis relative to the standard one. These distortions must be relevant to decisions informed by IQWiG, not to broader constituencies.

2.3.2.2 Time Horizon

The time horizon with respect to costs refers to the segment of the course of illness for which the costs will be accrued. This may be defined in various ways and is very specific to the condition at issue and the health technologies considered. It is crucial, however, that the period chosen covers a sufficiently broad period that all relevant costs are included and that all selected health technologies be assessed over the same period. For example, for an acute painful syndrome, a very short time horizon may cover all relevant aspects, especially if there are no sequelae and none of the therapies change the recurrence rate; while a much longer period is needed to assess a vaccination programme, or treatment of chronic diseases, as their consequences can stretch for years or decades.

The time horizon for cost estimation need not be limited to the periods for which there is evidence on the health technologies' benefits. Although there may be good reasons to limit the evidence-based assessment of benefit to just those periods, determination of the cost time horizon must be driven by the imperative to address the costs realistically and fully and avoid the biases that result from inappropriate curtailing of the period. It is understood that this may require projecting the course of illness over broader periods than strictly covered by the evidence-based medicine assessments but this is done in order to avoid distortions in the cost

estimates, not to create new health benefits for which evidence does not yet exist. Sensitivity analysis should be used to evaluate the effect of the time horizon on health benefits and costs.

A time horizon that is relevant for cost estimation may be discrepant with the one implied on the benefit side as a result of the evidence on which those estimates were based. This discrepancy can introduce substantial distortion if it is not resolved. The cost time horizon must not be reduced to match one determined by the duration of clinical trials because this will provide decision-makers with inappropriate information. For example, the clinical trials of a new stroke intervention would typically address disability three months after the stroke [24] and, thus, this is the evidence on which the benefit would be based. The majority of the costs of managing patients after stroke, however, occur in the following years [25].

The choice of time horizon must be carefully documented and justified in light of the specifics of the therapeutic area and health technologies. For each therapeutic area, IQWiG must define the time horizon for costs, and if discrepant with the one implied by the benefit estimates, must resolve the discrepancy by extending the time horizon or justifying why this is not done. Plots on this axis should reflect present value of the estimated financial streams and thus future values must be discounted appropriately.

2.3.2.3 Cost Parameterization

In order to estimate the costs of each intervention and plot them on the efficiency frontier graph, several choices must be made. The costs should be those that would be incurred in actual practice because these best reflect what is relevant in the decision. They should be presented on the efficiency frontier plot in terms of the total net cost per patient treated as that is easier to estimate and understand.

2.3.3 Plotting the Frontier

Recommendation:

An efficiency frontier should be plotted consistent with the definition given above.

Once the axes have been defined, the efficiency frontier graph can be plotted. The basic approach is quite simple. Each selected therapy is plotted at the intersection of its value assessment and its cost estimate. The remaining step is to draw the efficiency frontier itself

and carrying this out depends somewhat on the context for that particular therapeutic area and on whether the theoretical frontier will be used or extended dominance will not be considered.

2.3.3.1 Multiple Health Technologies

If multiple health technologies have been selected for the evaluation (or are already part of the efficiency frontier plot for that therapeutic area) then tracing the theoretical efficiency frontier is straightforward.

The first segment of the theoretical efficiency frontier goes from the no-intervention point to the intervention that produces the most value per unit cost (i.e., the steepest positive slope). This will often be the least expensive intervention, but may occasionally be another one that though more expensive, provides even more value per unit expense. The correct choice can be determined graphically by sweeping a radius from the vertical axis clockwise until it encounters a plotted intervention. That will be the first point on the efficiency frontier (Figure 2-8).
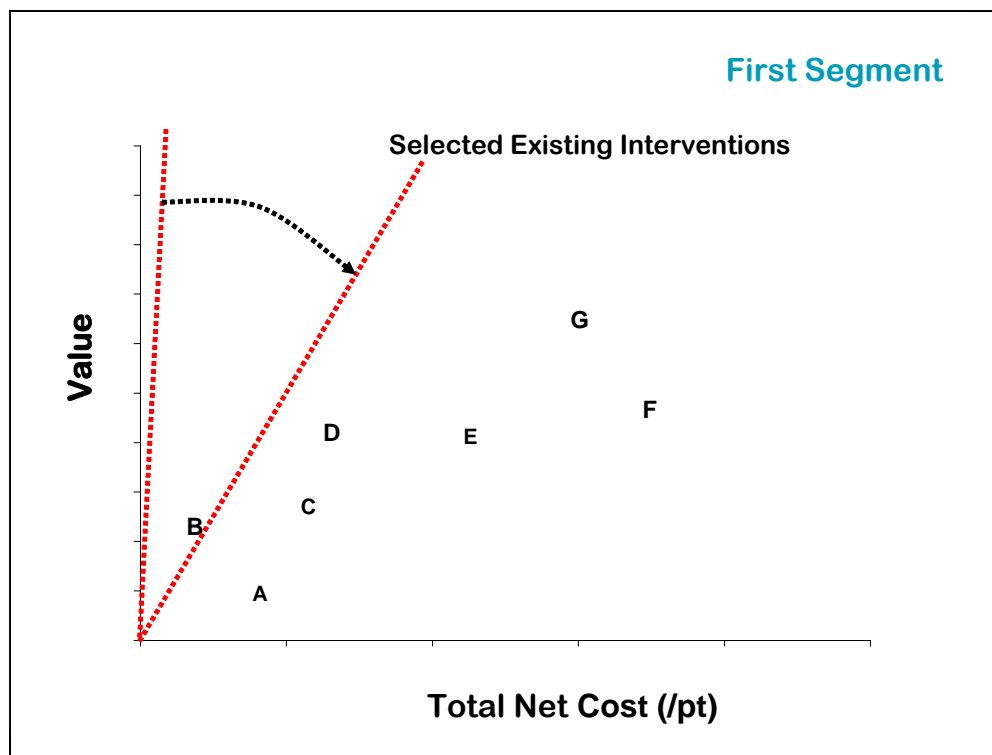

Figure 2-8 Selecting the first point on the theoretical efficiency frontier. The figure illustrates the clockwise sweeping of a radius from the vertical axis until it hits a plotted intervention, which is then the first point on the theoretical efficiency frontier. Intervention A is now definitely excluded because it provides less benefit at higher cost.

The no-intervention point also requires some assessment. Although, it might be taken to be the origin (zero benefit and zero cost), this is rarely appropriate as the absence of intervention may still produce costs and health effects (negative) due to the untreated illness, monitoring and so on. This can be taken into account by shifting the axes so that "no intervention" is at the origin. (Figure 2-9). This simply involves netting out the no-intervention amounts from the benefits and costs of the selected health technologies.
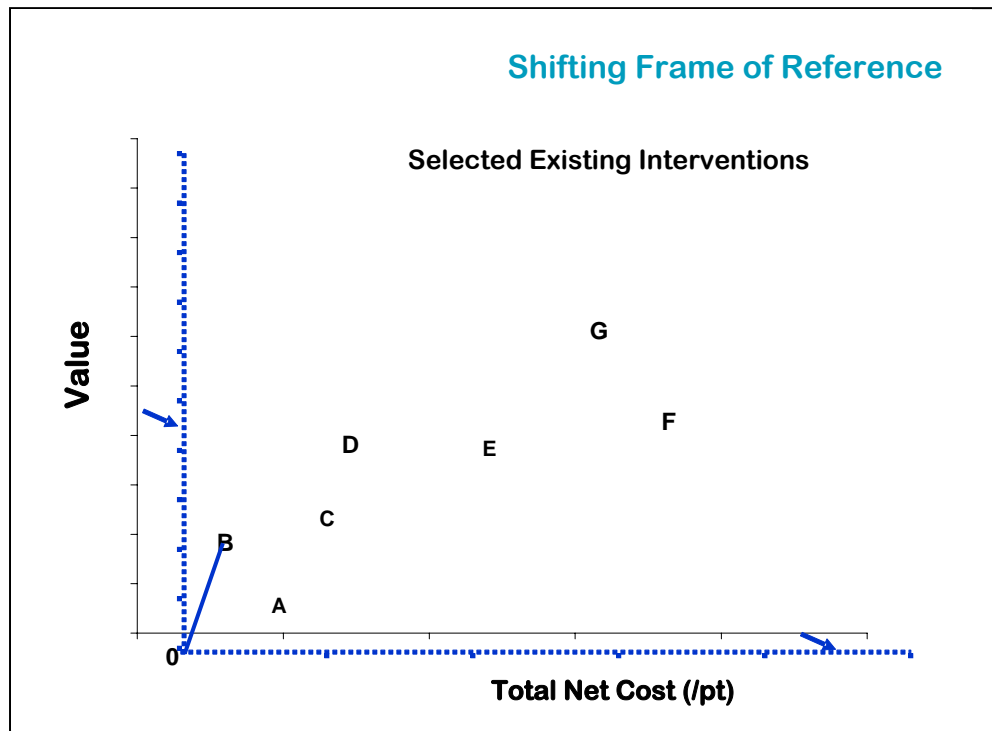

Figure 2-9 Shifting of the coordinate system to address a no-intervention point that accrues costs and has negative health effects. The first segment of the theoretical efficiency frontier is then drawn from this new origin to the first intervention identified by the clockwise sweeping radius.

If there are multiple existing health technologies to plot on an efficiency frontier graph, then the segment from the non-intervention point to the first intervention on the frontier is not so important and can be omitted. It is important, however, that the frame of reference (coordinate system) be clear and consistent for all the health technologies to be addressed.

After the first intervention on the theoretical efficiency frontier is plotted, the remaining health technologies are assessed in order of increasing cost to determine whether they provide more value than the first one. Among those that do, the one with the next highest value per unit cost (i.e., with the highest remaining slope) is selected and a segment is traced joining it

to the first one. Again, this can be accomplished graphically by shifting the radius to the first therapy and sweeping it clockwise until it hits the next intervention (Figure 2-10).
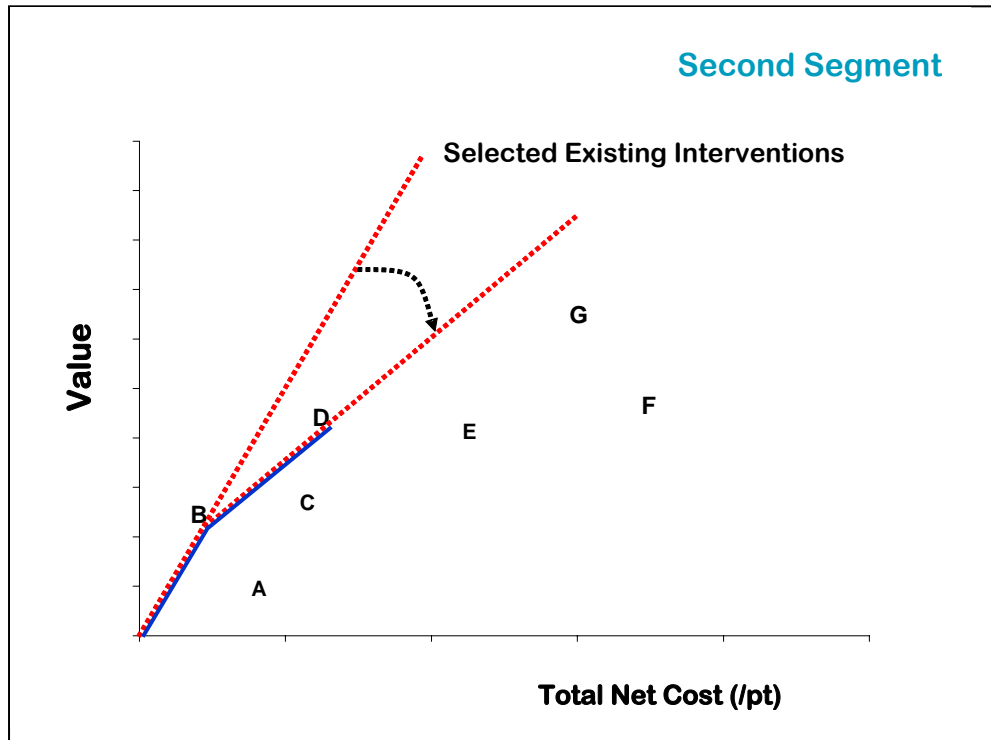
Figure 2-10 Continuing to build the theoretical efficiency frontier by resuming the clockwise sweep of the radius until it hits another intervention; and drawing the next segment between the first intervention identified and this one. Note, intervention C is now also eliminated in theory as any combination of use of health technologies B and D will provide more value for a given cost than C will. In practice, this extended dominance may not hold, leading to a concave section with segments from B to C and C to D.

This process takes place until no further health technologies with a higher benefit remain (Figure 2-11).

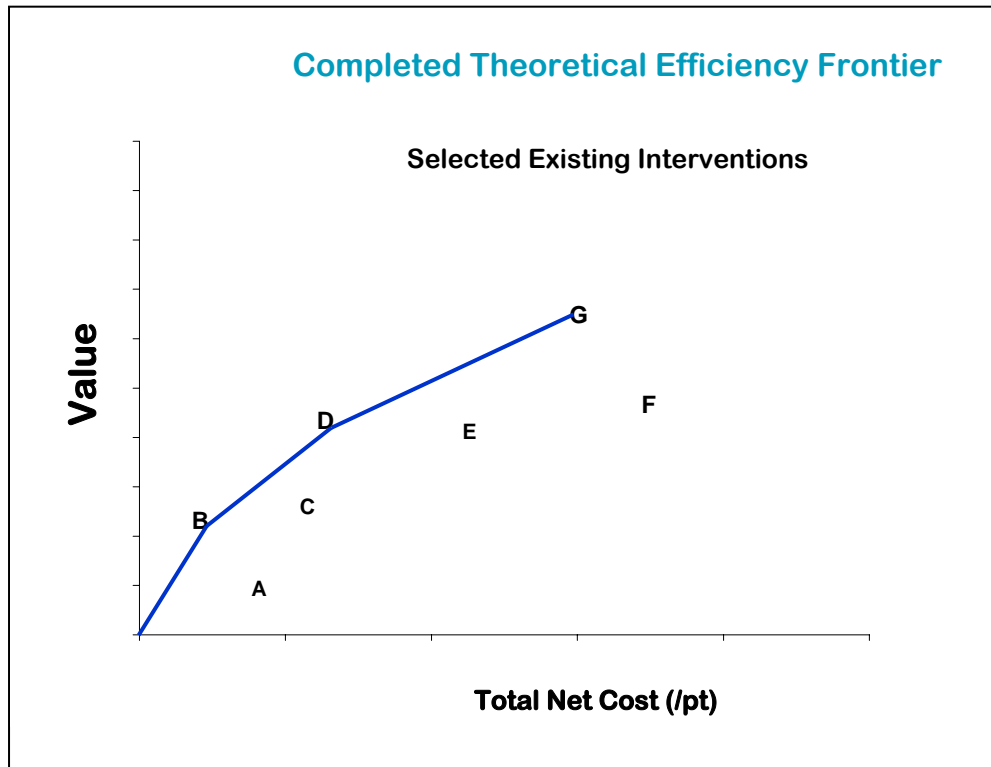**Figure 2-11** Completed theoretical efficiency frontier. The continuing clockwise sweep of the radius hits intervention G next and the segment between D and G is drawn. No other health technologies are part of the frontier because all remaining ones (F) have lower benefits.

Any new intervention would now be considered in light of the efficiency frontier (see Section 2.4).

2.3.3.2 Single Other Intervention

In some situations, there may not be multiple therapies selected for the evaluations. This may occur when an efficiency frontier for the particular therapeutic area has not yet been drawn and only one comparator is selected during the benefit assessment because none others meet the criteria. It may also be a legitimate depiction of all available comparators in an area where only one novel therapy has been available so far.

When only a single comparator intervention exists, the process of drawing the theoretical efficiency frontier is the same as for multiple selected health technologies except that it is now essential to draw the segment between no intervention and the existing one as that will be the only one available (Figure 2-12).
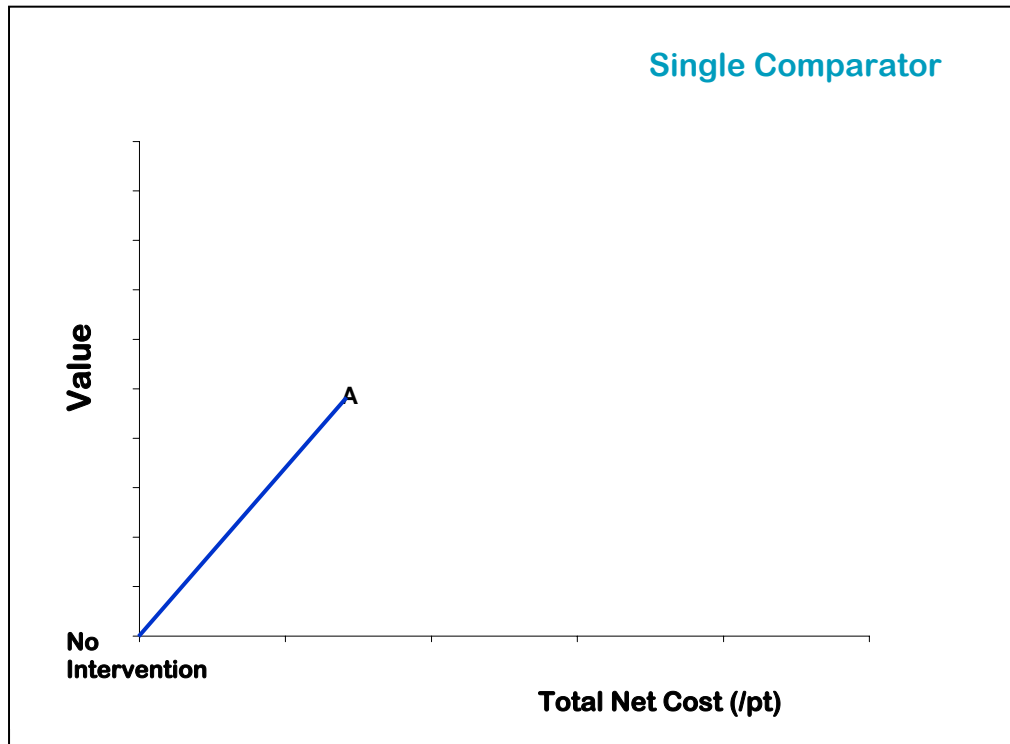
Figure 2-12 Efficiency frontier with a single available comparator, with the frame of reference re-centred on No Intervention.

This single-comparator efficiency frontier amounts to computing the ratio of the net value produced by that intervention to its net costs (both vis-à-vis no intervention).

2.3.3.3 No Existing Intervention

In the evaluation of a novel therapy, the situation will likely arise where there are no existing health technologies to plot on the efficiency frontier graph. In this setting, the new intervention will, by definition, set the first point on the efficiency frontier; and if it is reimbursed at the analysed price, then all subsequent therapies will be judged against its slope with respect to no intervention (see preceding section).

2.4 Decision Guidance Zones

The central purpose of the analytic framework is to facilitate decision-making regarding a ceiling price by presenting key information in a clear quantitative way. Although the ultimate decision involves considerations beyond those incorporated in the formal analyses, it is very helpful if the information presented within the framework provides guidance to the decision-maker.

The points along the frontier indicate the net cost at which a given level of value is being provided in Germany at that time. They point to what is possible to achieve in that therapeutic area. In other words, for a benefit of a given value, the frontier denotes the net cost that is consistent with the current market. Prices that place an intervention to the right of the efficiency frontier indicate a lower efficiency and thus require additional justification. The efficiency frontier itself, with no projection, allows decision-makers to examine the existing interventions in relation to each other and to address whether the system is operating efficiently in that therapeutic area.

Decision makers may choose to use this "expectation" as guidance in two ways: On the one hand, they may say that a new therapy with a given level of value below the highest one should be able to be sold at a price that is consistent with the efficiency frontier, unless documentation to the contrary is given. On the other hand, if the price is such that the therapy is above the efficiency frontier, it is in a sense performing better than one could expect and there is thus less reason to dispute the price. The plot also shows clearly inefficient interventions (i.e., those that are both more costly and less valuable than other existing options). In principle, questions may be raised as to whether the prices of such options need to come down if they are to continue to be covered fully by the SHI. For interventions that are not on the efficiency frontier but are not "absolutely" dominated, the guidance would be that their price seems too high and should, if possible, be brought in line with the efficiency frontier.

The actual decision on a ceiling price should incorporate other aspects that might matter (including the budget impact, the uncertainty surrounding the results, the importance of the technology) and these other considerations should be made explicit and quantified as far as

possible. Methods for the estimation of budget impact are provided in Section 4 and a technical document addresses the quantification of uncertainty.

If both the costs and the value produced by the newer intervention are higher than those already on the plot, as is typically the case, it is not clear what should be done. Now, there must be some external criterion imposed to judge the reasonableness of adopting the beneficial, but more expensive, newer intervention.

The external criterion for reasonableness could be imposed by the decision-makers themselves in terms of the willingness of insured German citizens to pay for a particular benefit in a given therapeutic area. This would involve obtaining these valuations from representative German citizens using survey or other techniques [26]. If this is provided by the decision makers, then the guidance is simplified to estimating at what ceiling price the new intervention is consistent with the external standard.[6]

In the absence of an external standard, guidance for the decision-maker is accomplished with the efficiency frontier by dividing the space into several *decision-guidance zones*. According to the zone into which the intervention falls, clear guidance can be given to decision makers. This can then be incorporated into the broader process of decision making and setting a ceiling price.

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[6] It should be note that an external willingness-to-pay standard may indicate that all, or many, of the interventions in a therapeutic area are priced inappropriately or are acceptable.

2.4.1 Boundaries

Recommendation:

The area of superiority is demarcated by the horizontal line intersecting the point of the intervention that gives the most value.

The area of higher costs is demarcated by the vertical line that intersects the most expensive therapy.

There are three key boundaries that define the decision zones. The main one is the efficiency frontier itself. The other two boundaries are the current maximum value produced and the highest prevailing cost. The current maximum value boundary should correspond to superiority according to IQWiG criteria.[7] The highest prevailing cost boundary situates health technologies according to the direction of their expected net cost impact.

2.4.1.1 Superiority

The superiority boundary is established by drawing a horizontal line from the vertical axis to the selected existing intervention that produces the most value in the therapeutic area at issue (Figure 2-13).

All health technologies below this line are inferior to the best available one; and all above it are superior. According to current IQWiG practice, only newer health technologies that are above the line will be the subject of economic evaluations (but the Method is fully applicable below the line as well).

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[7] It is possible, though it should be quite rare, for a new intervention to offer superior benefits and yet not offer greater value — if those additional benefits have no value (or even negative value).
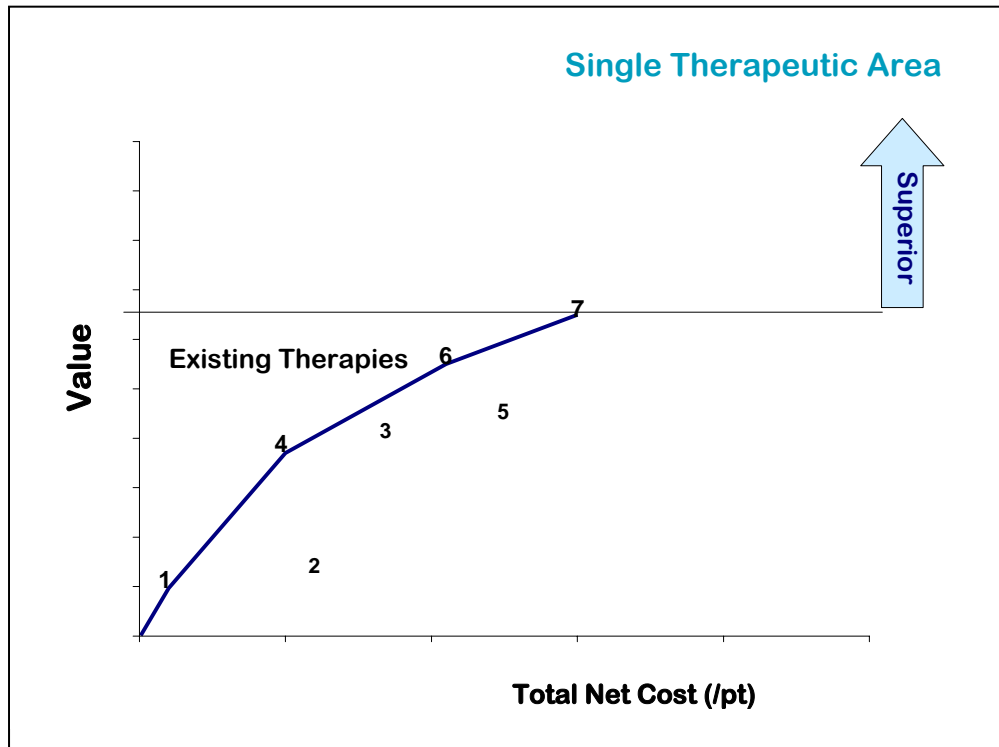
Figure 2-13 Establishing the superiority boundary.

2.4.1.2 Highest Prevailing Cost

The boundary given by the highest prevailing cost is set by drawing a vertical line from the horizontal (i.e., *cost*) axis up through the point identifying the intervention with the price that yields the highest cost.[8]

Health technologies to the left of the highest prevailing cost boundary are priced such that they are less costly to use than the most expensive one already reimbursed in Germany, and any new health technologies priced so they are to the right of the boundary are more expensive (Figure 2-14).

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[8] Usually, this will also be the one with the superior benefit, but not necessarily if the system is operating inefficiently.
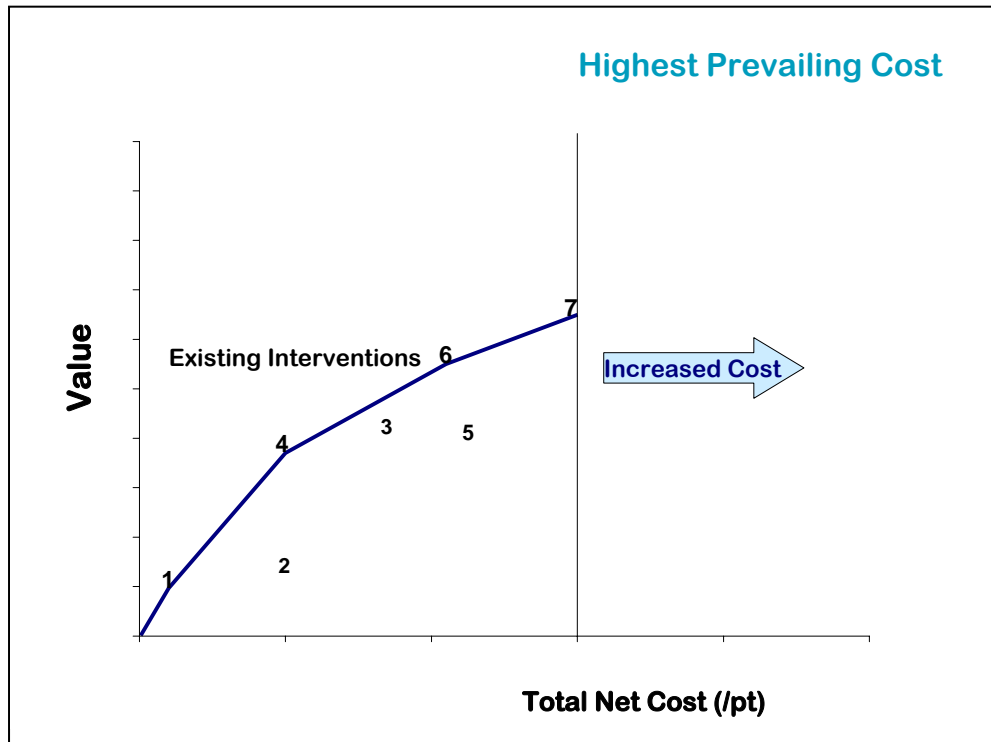
Figure 2-14 Establishing the highest prevailing cost.

2.4.2   Above Superiority Boundary

Recommendation:

- **Health technologies falling in the decision zone indicating superiority, with prices that yield costs lower than the highest prevailing one, should continue to be reimbursed at the prevailing price (and they redefine the theoretical efficiency frontier).**

- **Health technologies in the area of superiority but with prices that indicate higher costs require further assessment of their price to ensure reasonableness. If the amount of value produced relative to the costs is:**

  o **better than all existing ones, they should continue to be reimbursed at the prevailing price (if judged affordable).**

  o **less than the lowest efficiency on the efficiency frontier their price should be reassessed in terms of what is judged to be acceptable for German citizens in that therapeutic area as determined by the appropriate body designated by law.**

> o **on the projected efficiency frontier, the prevailing price may be appropriate (if judged affordable).**

The area of most relevance to IQWiG is above the superiority boundary as this is where most, if not all, the economic evaluations are to be carried out. The decision zones in this area are also demarcated by the highest prevailing cost line but there is no longer an established efficiency frontier to provide additional guidance as this zone is above the area demarcated by the selected existing therapies (Figure 2-15).
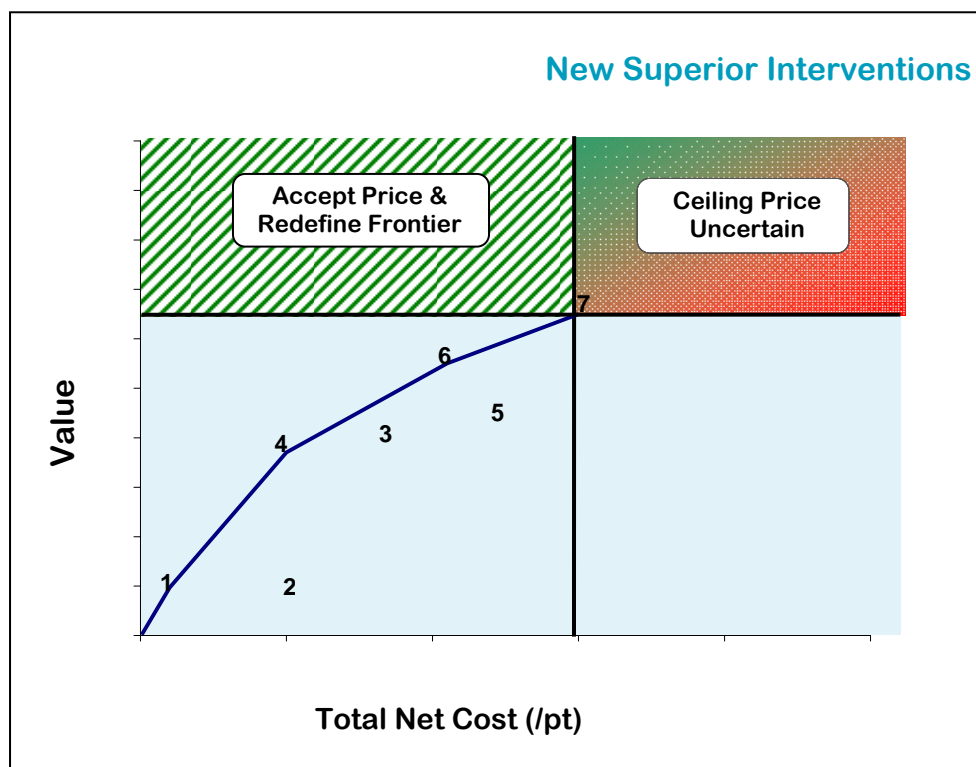
Figure 2-15 Decision zones above the superiority boundary.

2.4.2.1 Below Highest Cost

In this area lie superior health technologies which are priced in such a way that they result in net total costs below the highest prevailing cost. This is clearly an attractive area and, from an economic point of view, continued reimbursement at the prevailing price should be recommended (Figure 2-15). Any new intervention in this area also redefines the theoretical efficiency frontier. Indeed, the question arises whether other existing health technologies still deserve to be reimbursed at their extant prices (Figure 2-16).

Figure 2-16 Superior therapy "A" has a lower total cost than the highest prevailing one and redefines the theoretical efficiency frontier, putting prices of the circled therapies in question.

2.4.2.2 Above Highest Cost

The area above the superiority boundary and to the right of the highest prevailing cost does not provide as clear guidance for decision making because new health technologies plotting in this area are in a zone with no prior referent — they excee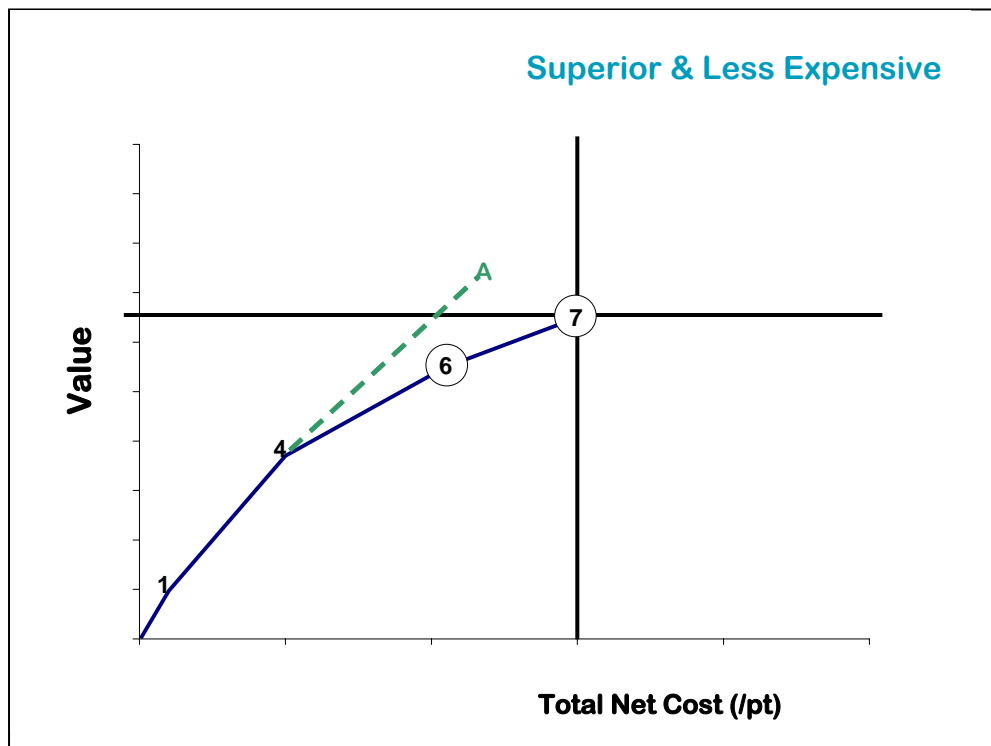d both health and cost consequences of existing therapies. Unfortunately, most new health technologies will appear in precisely this area.

One option for this zone is to fund all health technologies appearing in it on the grounds that they are superior to all existing therapies. This is clearly not a sustainable approach, however. At the extreme, health technologies offering only very small improvements in benefits could set extremely high prices (i.e., slope just above the horizontal) and still demand reimbursement under this decision rule. Such an approach would lead to massive inflation in the health care sector.

Another approach would be to refuse funding of all health technologies plotting in this zone given that they increase costs to the system. This is just as unreasonable an approach as funding all of them. Again, at the extreme, it would reject therapies providing massively more value at very small increases in total cost (i.e., slope just less than vertical). Thus, there is a gradient of acceptability going from almost certainly appropriate at the near vertical to almost certainly inappropriate at the near horizontal. The reasonableness of prices for those health technologies in between must be assessed by those designated by law to do so. This need not be done in a vacuum, however. Some guidance can be provided to those charged with making this assessment. That guidance is also based on the efficiency frontier.

The theoretical efficiency frontier reflects the set of health technologies that will produce the most benefits for a given total cost. If there is a single existing intervention on the frontier, then the ratio of its net value to its net costs (with respect to no intervention) is the current efficiency rate in that therapeutic area.[9] A new intervention that is both more beneficial and costly than the single existing one can now be assessed relative to the efficiency of the accepted intervention (Figure 2-17): it is either more efficient (above the projected slope of

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[9] Note that this is just the "going rate". While it does not mean that this is a reasonable rate, it is what the German system is paying at that moment for the value of those benefits.

the first intervention); equally efficient (on the projected slope); or less efficient (below the projected slope). Thus, designated bodies called upon to address the reasonableness of prices of health technologies falling in this zone for this therapeutic area could use that projection as guidance. It should be noted that doing so implies acceptance of previous pricing decisions. Decision makers should consider this given that many such decisions, especially in the early years of economic evaluation, will not reflect explicit assessments following these Methods.
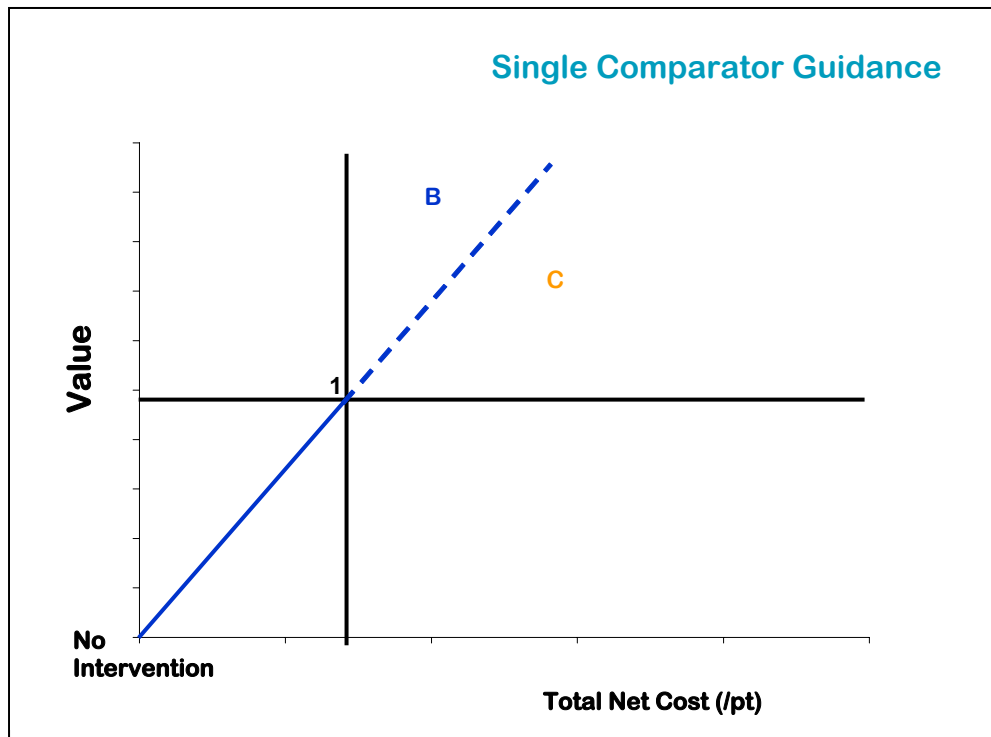
Figure 2-17 Developing guidance for new health technologies that both provide more value and are more costly than a single existing intervention in a particular therapeutic area. The dashed extension of the existing efficiency frontier divides the decision zone into a more efficient area (B) and a less efficient one (C).

When there is more than one selected existing intervention on the efficiency frontier, there are more options for developing the guidance regarding health technologies that are both more costly and beneficial. The simplest approach —consistent with the efficiency frontier methodology — is to extend the last segment of the theoretical efficiency frontier into the decision zone (Figure 2-18). This last segment reflects the lowest incremental efficiency on the existing theoretical efficiency frontier. The projected line segment indicates the maximum price that would be consistent with information available in the current market. Prices above

that would imply accepting a lower efficiency and thus would require added justification. The manufacturer would need to give good reasons for not being able to meet the efficiency implied by existing interventions and the decision makers would have to consider whether these sustain the proposed price.

Analogously with the context of a single existing intervention: those above the simple projection of the theoretical efficiency frontier are incrementally more efficient than what has already been accepted for the next best intervention; those on the theoretical efficiency frontier are incrementally equally efficient; and those below it are less efficient (in absolute or extended form) at their current price.
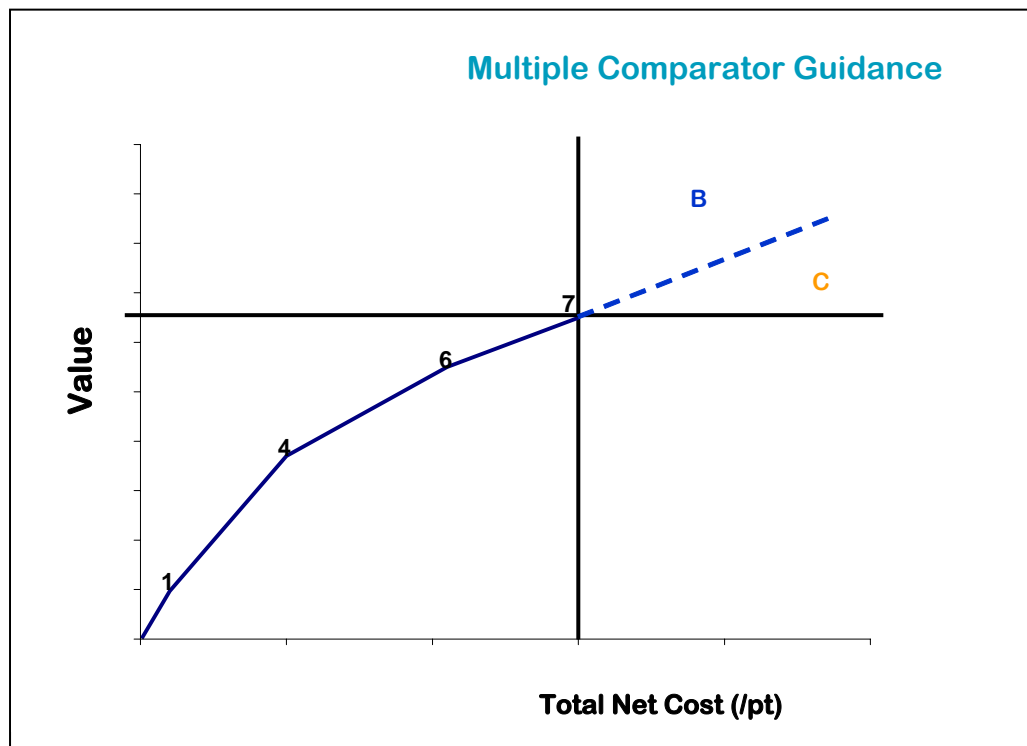
Figure 2-18 Simple projection of the theoretical efficiency frontier[10] to provide guidance for assessment of reasonableness of new health technologies that are both more costly and beneficial in a therapeutic area with multiple existing health technologies. The dashed extension of the theoretical efficiency frontier divides the decision zone into an incrementally more efficient area (B) and a less efficient one (C).

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[10] If there is an option in the triangular area of extended dominance between options 6 and 7, then projection for guidance may need to take this into account.

Although this approach to using the efficiency frontier for setting a ceiling price for a new, superior intervention yields a clear comparison with the existing situation, it is emphasized that this can only provide guidance, not a decision rule. It is quite possible to reject a new intervention that is more efficient on the grounds that the increased expense is not reasonable in that therapeutic area; it is equally possible that the price of a less efficient intervention is judged reasonable because the added benefit is thought to be worthwhile despite the disproportionate increase in cost.

Although alternative approaches to providing guidance can be derived, it is not clear what the conceptual foundation would be for these methods that do not directly project the efficiency frontier. If any of them are implemented in a particular therapeutic area, then the choice will need to be carefully documented and justified. In no case, however, should an arbitrary boundary be drawn [27,28] . This has no justification and can lead to poor decisions with no rational basis [29].

The slope of the efficiency frontier decreases from left to right. This follows from the way the EF is constructed, but in a therapeutic area with enough observations to show a trend, the decreasing slope may also be seen as reflecting diminishing marginal returns (i.e., the fact that even in the subset of "most efficient therapies", increases in costs of development and production provide less and less additional value). The efficiency frontier shows the rate of this decline in marginal returns. The rate of decline indicates "what is to be expected" in terms of cost increases for new therapies that provide more value than earlier ones. It must be borne in mind that in an area with few competing therapies, there is less ground for interpreting the efficiency frontier in this way.

Another interpretation of the efficiency frontier is possible if the price of the last (best and most expensive) therapy on the frontier is the result of public evaluation and decision in a comparison with the price of the second best therapy on the frontier. If this has been the case, the last line segment of the frontier indicates the marginal willingness-to-pay for increased value in the intervention area in question. A new therapy that yields a better incremental value-to-cost ratio than this (relative to the previously best therapy) may *a priori* be said to be consistent with revealed willingness-to-pay. Decision makers would still need to consider whether previous willingness-to-pay continues to apply as new more costly technologies are developed.

The proposed use of the efficiency frontier does not address societal preferences regarding the funding priorities across diseases because IQWiG did not take this to be in its mandate. This is left to the decision makers charged with that responsibility in the German system. It should be noted, however, that if those decision makers wish to make their priority-setting explicit, they can do so by setting a budget for each therapeutic area (and providing the corresponding rationale). By doing so, the efficiency frontier plot gains an additional limit and further guidance can be provided, particularly for interventions that yield superior benefits but at increased cost.

2.4.2.2.1 Better Efficiency

Superior health technologies with a price that places them above the projected efficiency frontier or other guidance line produce equal or more value for a given incremental cost than the next best one. Unfortunately, the total cost implied represents an increase beyond the highest prevailing cost and, thus, reimbursement of these health technologies requires additional funding for the given therapeutic area.[11] Hence, the assessment of health technologies in this area is primarily a budget impact consideration. The designated gremia charged with judging the reasonableness of funding such an intervention must evaluate the additional funding required (see Section 4). Whether it is justified to spend that on a particular therapeutic area is a consideration that lies outside the mandate of IQWiG and involves many aspects beyond efficiency estimates.

2.4.2.2.2 Equivalent Efficiency

Health technologies that lie on the projected efficiency frontier provide additional value at a rate consistent with that of the existing health technologies on the efficiency frontier: they neither redefine the frontier, nor are they dominated by the projection. Thus, they have a solid basis for the current price. Still, decision makers must assess whether it is reasonable to continue with the extant price, taking into account the required increase in the budget and other considerations noted above.

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[11] Note, there is also the option of reallocating funding within the area to redistribute resources that are being spent on less efficient health technologies.

2.4.2.2.3 Worse Efficiency

Health technologies that are superior but so much more costly that they lie below the projected efficiency frontier pose a problem. Although they provide more value, they do so in a less efficient way than existing health technologies. Thus, accepting to reimburse such an intervention at the requested price involves a further reduction in the standard for that therapeutic area. This would extend the efficiency frontier to a lower position and make it even easier for yet another health technology to enter in a desirable position. Whether it is reasonable to allow this extension is a matter for the insured citizens to assess. It involves consideration of the magnitude and importance of the benefit as well as of the budget impact.

SECTION 3

3 Estimation of Costs

As there are many local factors that influence the estimation of costs, this must be carried out in a specific context. Unlike estimates of efficacy and safety, there is no general "cost" that will hold across time, place and other aspects [30]. To be useful to the decision maker as well as form the basis for inputs to an economic model, these estimates must be reported in sufficient detail, suitably modified to accord with the particular context at issue.

3.1 Definition

There are various theoretical aspects involved in defining a "cost" (these will be covered in the technical document). Here the focus is on the more practical issues.

Two main types of cost are distinguished in economic evaluations [31]. One type refers to the costs of those items for which there is a *direct* monetary payment. This payment need not take place in actual practice — it suffices that there is, in principle, such a payment. These ***direct costs*** are typically subdivided into those related to health care services ("direct medical costs") and those accrued by the patient, family and others ("direct non-medical costs"). Clearly, this subdivision is somewhat arbitrary and the specifics will vary from place to place and analysis to analysis. Moreover, patients and their families may pay a portion of the costs of health care services (e.g., through co-payments). A clearer categorization, unfortunately not often used in health economic evaluations, would be into "Insured" referring to those the payer covers and "Not insured"; referring to those borne by others regardless of what goods and services they are paying for. This terminology is used here.

The other main type is ***indirect costs***, which refers to those for which there is no monetary payment, even in principle. As the term "indirect" is used in some circles to refer to overhead costs, some have preferred to call this category "Productivity" costs, alluding to the main type of item - lost production - in the class.

A third kind of "cost" in economics is the *intangible* type, reflecting the value of suffering, stress and diminished quality of life. As noted above, these items are typically not considered on the cost side in health economic evaluations.

3.1.1   Insured Costs ("Direct Medical Costs")

Recommendation:

Insured costs should be considered in economic evaluations carried out on behalf of IQWiG.

Insured costs reflect the monetary value of the health care resources that are consumed during the provision of a particular heath care service and are covered by insurance. Typical examples are the cost of a physician visit, of a hospital stay, or of a laboratory test. These costs are what payers cover and thus are the cornerstone of health economic analyses, as evidenced by their prominence in the guidelines of many countries and agencies [32-34]. For example, the guidelines produced by the Government of Australia [35] state that "direct medical costs" must be included in their economic analyses while indirect costs are discouraged. A similar emphasis on insured costs exists in Finland [36] and Italy [37]. Even in countries such as Germany, where a broader perspective has been encouraged [2,38], many studies include only insured costs [39-42].

3.1.2   Not Insured Health Care Costs ("Direct Non-Medical Costs")

Recommendation:

Health care costs not covered by insurance should also be included.

Health care costs not covered by insurance, often referred to as out-of-pocket expenses, are those that are not paid for by the third-party payer. These may include co-payments, over-the-counter medications that are not covered and transportation for visits. These costs are usually borne by patients and their families and may be significant. In Germany, a portion of the costs traditionally thought of as "out-of-pocket" are covered by the Sickness Funds [43], and thus form a part of the insured costs and should be addressed in IQWiG's economic evaluations [44,45]. Indeed, during the period from 1992 to 2002, the out-of-pocket portion of health expenditures rose from 10.7% to 12.2% in Germany [46].

In one study designed specifically to address the patient's perspective, the proportion of direct costs borne out-of-pocket was estimated. The investigators reported this to be 15.3% of the direct costs for rheumatoid arthritis care [44]. Figure 3-1 provides the distribution by category

and shows that the bulk consists of non-physician services (e.g., therapists), medications and transportation.
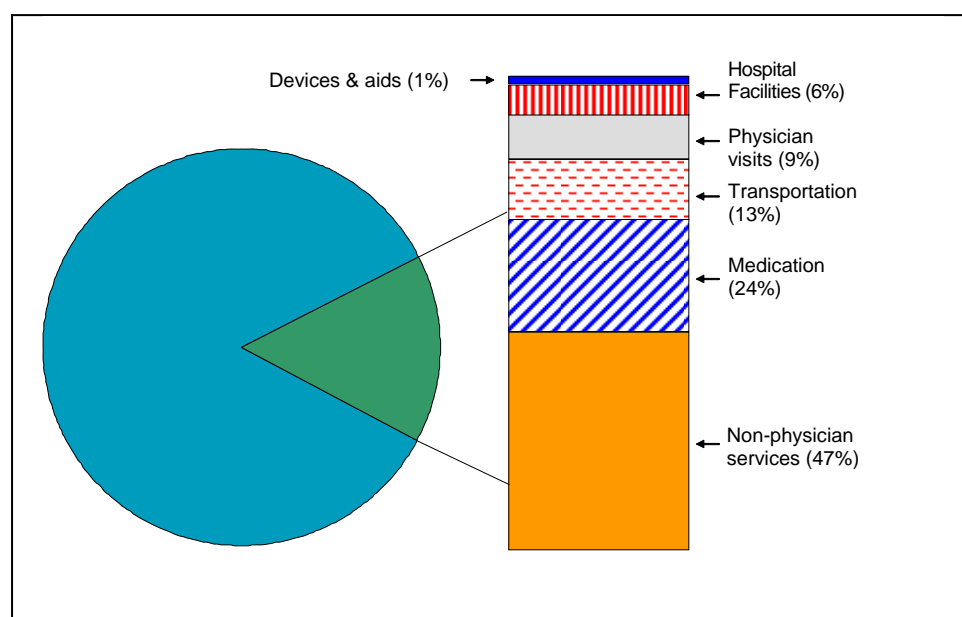
Figure 3-1 Types of out-of-pocket expenses and proportion of direct costs for management of rheumatoid arthritis in Germany (based on data from [44]).

It could be argued that only the portion of direct non-medical costs covered by the SHI (and thus part of the Insured Costs) should be included in evaluations carried out for IQWiG. As the perspective is that of the insured citizens, however, all direct costs borne by them should be included.

3.1.3 Indirect Costs

Given the purpose of economic evaluations conducted on behalf of IQWiG, it is not recommended that indirect costs be included, at least not as a "cost" item. If productivity losses are substantially affected by a new health technology, consideration could be given to including them as a health "benefit" side, although this is controversial [47].

3.2 Approach

Four basic steps are required to estimate the costs of a condition: identification of the resources consumed, quantification of that consumption, valuation of each resource in terms of the cost per unit of consumption and putting it all together to reflect properly the management of that condition in a specific context. Although, in principle, all of these steps could be carried out within a single data collection study, this is rarely possible in practice. Instead, it is usually necessary to gather cost-related pieces of information from a variety of sources. Determining which sources to use is always a balancing act between relevance, credibility, and availability [48].

The first two stages relate to the process of creating a resource use profile, the third to applying unit costs. In the identification stage, the types of health care services that are used for managing the condition need to be identified. In other words, the answer to the question, "W*hat health care services (resources) are used by the patients with this clinical problem?",* must be determined. Definition of the resource use profiles usually begins with the opinion of clinical experts — they are asked to identify the types of resources that are typically consumed in managing a given condition. These initial profiles must be supplemented by actual data obtained from whatever sources can be found: hospital discharge data sets, other claims databases, government and other agency reports, practice guidelines, and peer-reviewed medical literature.

3.2.1 Identifying the Resources

Recommendation:

Identifying the resources that are to be included in the costs requires specifying the perspective, selecting a time frame for the analysis and determining the cost centres. Expert opinion may be valuable in these tasks.

3.2.1.1 Perspective

In accord with the law, the perspective of the citizens insured by the SHI in Germany (*Versichertengemeinschaft*) will be adopted for the estimation of costs. This perspective implies that all insured costs will be included plus all those costs related to health care that are not insured but are a substantial component in a given therapeutic area.

3.2.1.2 Time Frame for the Cost Estimates

The time period over which the cost consequences are to be considered will also dictate the extent of the costs that will be counted. The time horizon should be appropriate for the condition and sufficiently long to capture all relevant cost considerations related to the health technology or program [33]. For example, as the costs of treating patients with stroke after the acute hospitalization can be responsible for the largest proportion of expenses [25], the time period for this event should not be limited to the acute phase alone.

3.2.1.3 Cost Offsets

Although the immediate costs of new health technologies often exceed the costs of existing technologies, these increased costs might be offset by savings in other areas of the health care system. A cost offset is therefore a decrease in resource use that can be attributed to a particular health technology, though it is typically in cost areas other than the health technology itself. Those resources for which a decrease in consumption may occur should also be identified and quantified. If a cost-offset claim is made using an observational study, or the cost-offset is obtained by extrapolating the clinical effects observed in a randomized trial, the impact of the cost offset should be investigated in comprehensive sensitivity analyses.

3.2.1.4 Costs in Added Years of Life

If extension of life is germane to the economic evaluation, the costs of managing the illness at issue during the added years of life should be considered in an entirely separate analysis as they address a different question. Full explanation of the methodology and sources used to prepare the estimate must be provided and the implications of including these costs should be discussed.

3.2.1.5 Start-up Costs

In order to implement use of a new health technology, it may be required to fund one-time activities. These start-up costs should also be identified and quantified. They should be reported separately, by category, in the budget impact analysis (see Section 4) with a full explanation of the methodology and sources used to prepare the estimate.

3.2.2 Quantifying the Consumption

Recommendation:

Quantification of consumption of resources must be based on actual data that are credible and relevant. Expert opinion is not to be used for this task.

The quantification phase deals with establishing the frequency of use, the proportion of the relevant patient population that used each service and the duration of that service — all of which may increase or decrease in any given situation. Identifying the frequency of service use is often easier than finding the proportion of persons using the service, but it is essential to apply the cost to as accurate a rate of users as possible. Assumptions of use can lead to extremely imprecise cost estimates, particularly for conditions where the person may be treated as either an outpatient or inpatient. An example will be provided in the technical document.

It is recognized that it may often be necessary to compromise when using available information, particularly regarding newer interventions, but the overriding consideration must be to base the quantification on data that are credible and most appropriate for the analysis — not just the information that is most readily available. While expert opinion may be useful for determining which resources are involved in a given therapeutic area, is not appropriate to use the opinion of clinical experts in the actual quantification. Costs for items that are very infrequently used and are thus likely to have little impact on the results should be described, but not necessarily calculated [31].

Available approaches to quantifying resource consumption will be detailed in the technical document.

3.2.3 Valuing the Resources

Recommendation:

Either micro-costing or a top-down approach can be used to value resources but the choice must be carefully justified for the given therapeutic area.

Once the resource use profile is developed, it is then necessary to identify the appropriate unit cost for that service at the level required by the model and apply a cost to each resource

identified in the profile (valuation phase). The approach to estimating the "unit" costs in order to value the resources consumed can be bottom-up (micro-costing) or top-down. In the bottom-up approach, the unit costs are estimated alongside the micro-costing study by obtaining the salaries including benefits, the prices paid for supplies and so on. Starting with an aggregate cost to derive a unit cost per patient by dividing the total cost by the volume of services provided reflects a top- down costing approach. A study published in 2003 that examined the economic burden of obesity in Germany used this approach [49].

The alternative most frequently employed is to accept the profile at whatever level of aggregation is accessible. For example, one of the most easily obtained is the average cost of a hospital stay based on the published costs by Diagnosis Related Group (DRG). Unfortunately, although easier to find, this type of estimate has a serious deficiency for economic analysis as few DRGs are sufficiently disease- or procedure-specific; they aggregate at a much higher level and any given DRG may reflect several conditions, some of which have little to do with the disease of interest.

3.2.4   Calculation of the Costs

Recommendation:

A model of the disease and its management should be used to calculate the total net cost of each health technology. Patient-level simulation is the preferred technique. The model must be

- **fully transparent, with model inputs and assumptions defined and justified;**

- **of sufficient depth to adequately represent the disease being modelled and the costs associated with it and the health care treatments at issue;**

- **flexible enough to assess multiple scenarios under varying sets of assumptions and settings;**

- **allow for an assessment of uncertainty in predicted costs;**

- **populated with data that are relevant to Germany, including not only costs, but also clinical practice patterns, demographics and epidemiology;**

- **fully validated in terms of its accurate representation of the disease and its management, the integrity of internal calculations, and its ability to reflect external data;**

- **rigorously peer-reviewed, with reviewers provided access to the relevant technical documents and to a fully functional and evaluable electronic version of the model.**

The cost of each health care service within the resource use profile is applied to the proportion of patients utilizing that service to derive the total cost for managing that condition or event. Full costing of a particular health technology requires detailed mathematical representation (modelling) of the disease or condition in terms of what may occur depending on what is done and valuation of the resources consumed. Patient-level simulation is the best approach for this type of modelling as it provides the necessary level of detail and imposes fewer restrictive assumptions.

Models are analytic tools used to understand real world systems, estimate outcomes for a given set of inputs and examine the effects of changes to the system being modelled. In effect, any evaluation that extends beyond direct application of observed data can be considered a model [50], and even direct application usually involves some form of statistical modelling. It is understood that models cannot represent reality perfectly: they are based on a reduced set of components and require simplifying assumptions. Nevertheless, it is crucial that the model be valid in the sense that it sufficiently reflects the system it represents. The technical document "Modelling" describes modelling approaches in health care and provides guidance on the process of developing economic models, preferred modelling techniques, and reporting of modelling studies.

3.2.5 Cost Factors

Recommendation:

All adjustments made in translating original data to cost estimates used in the economic evaluation must be reported (along with the original data). These include inflation from prior years, modifications to reflect the relevant perspective and discounting.

3.2.5.1 Inflation

The health services of many interventions are consumed at any time. Therefore the costs of these services have to be revised by inflation.

The year for the currency valuation used to report the costs must be specified. If not the current year, a reason should be provided for using an older currency valuation.

As there is often a time lag between the actual cost data and when they are used in an analysis, all cost data sources may not be from the same year. Thus, it is not uncommon for cost values to be inflated. Inflation should be used only when absolutely necessary and applied appropriately. It should not be used as a substitute for obtaining available current data. If used, the appropriate rate for the medical service at issue should be employed.

3.2.5.2 Discounting

The costs and benefits of health services occur often at different times. To compare the costs and benefits of an intervention both have to apply to the same point of time. Discounting formalizes the adjustment of future values to the "present value". It accounts for the differential timing of costs, weighting them according to when they are accrued. Discounting is an important technical aspect of economic appraisals of health-care health technologies as in most cases the expenditures related to health technologies are spread over time and may differ between alternatives.

Based on the nature of the costs that are modelled, appropriate discounting methodology needs to be applied for any future accruals. This may be discrete or continuous discounting or a mixture. Additional details will be provided in the technical document.

The choice of discounting rate has a significant effect on the results of the economic evaluation. Although various rates are given in health technology assessment guidelines [23,38,51,52], the appropriate recommended rate in Germany is at present 3% (see chapter 2.3.4 in the technical document Cost Estimation). As the choice of discount rate, even at the national level, is somewhat arbitrary, sensitivity analyses have to be performed in order to examine the sensitivity of the results to this cost factor. The results should be computed for discount rates of 0%, 5%, 7% and 10%.

3.2.5.3 Other Adjustments

Cost-related data can be reported in several ways. Generally, these data are thought of in terms of broad categories, such as the provider's cost (cost of delivering health care service), a submitted charge (the amount billed for the service), or a payment (reimbursement for the service). Charges may also be referred to as prices [53]. The health care system may dictate which term is used. One report that examined cost accounting methodologies in the German health care system [54] discussed cost assessment in similar, albeit not exact terms of "prices" and "costs". The "cost" was defined as the monetary value of the resources employed by the provider to deliver the service. Prices were defined as the total amount of money that a purchaser must pay for a particular health care service. As this definition includes any co-payment or deductible assumed by the patient for that service, it does not necessarily reflect the payment provided by a Sickness Fund. Any adjustment made, such as applying a cost-to-charge ratio, must be disclosed. The ratio value must be reported, along with the methodology and sources used to derive it, as well as the values to which it was applied.

3.3 Reporting

The perspective of the analysis should be stated clearly and defended. The time period should be described and the reason why it was chosen should be provided. All adjustment factors must be reported and justified.

All relevant insured and non-insured costs should be calculated and included in the evaluation. The latest data available from credible sources should be employed in all cost calculations. The source must be specified by formal citation, described fully and a statement as to why this is the best available source should be provided. In addition, the statement should provide information regarding availability of the data sources by including the following description as applicable:

- publicly available data (no fee for use),

- public data (fee for use),

- commercial data for purchase,

- published manuscript,

- published government/agency report,

- unpublished but available upon request.

If none of these descriptions apply, a statement that best describes the availability of the information for review by others should be provided.

A detailed description of the resource use profiles, as well as of the methodology used for developing the total cost estimates must be provided. Whatever estimation method is used to calculate indirect costs, these costs should be reported separately with full accounting of the cost content and method employed. This is essential so that those reviewing the findings can determine their relevance to the overall result of the study.

The report must also include generally accepted quality criteria for modelling, including details of the model including its influence diagram, patient flow, functional relationships, rationale for choice of technique, full listing of all assumptions, validation techniques and results, how uncertainty was dealt with, and limitations. Resource use and unit cost information pertinent for Germany should be standard for all economic analyses. If regional implementation is required, potential variation in results by region should be itemized and discussed. If German data are not used, a detailed explanation must be included and reasons for lack of German-specific values and justification for proxy data must be provided.

SECTION 4

4 Budget Impact Analysis

Even after a new health technology has gained a positive evaluation in terms of benefit, and has been shown to be on or above the efficiency frontier, it must still be affordable to the German payers [55]. To assess this aspect, requires and economic evaluation that considers the impact on budgets.

4.1 Definition

Budget Impact Analysis (BIA) is an assessment of the direct financial consequences of reimbursing a health care health technology in a specific health care setting [56] It is complementary to the comparative efficiency analyses that examine the benefit-to-cost ratios of health technologies. It evaluates the affordability and financial impact according to the potential rate at which existing patients will receive the new therapy ("uptake") and its diffusion across the health care system, including its use by previously untreated patients. In particular, a BIA predicts how a change in the mix of drugs and other therapies used to treat a particular health condition will impact the trajectory of spending on that condition.

It is necessary for healthcare decision makers to understand these budgetary consequences in order to make informed decisions. Taking into account the experiences of other health care systems, even citizens' committees that address the acceptability and reasonableness of a new expenditure need to understand what that expenditure might be. There may be circumstances where the efficiency analysis indicates an efficient technology — that is, one that meets or exceeds the efficiency frontier — while the BIA results suggest that affordability may be a problem. In such instances, there is no scientific guidance on how to resolve the dilemma [57].

4.2 Approach

The purpose of a BIA is not so much to produce exact estimates of the budget consequences of an health technology but to provide a valid computing framework (a "model") that allows users to understand the relation between the characteristics of their setting and the possible budget consequences of a new health technology (or even of a change in usage of current health technologies) [57]. Such a model is required because many of the elements vary from

place to place and there is uncertainty about them, even in a single place. Thus, there is not a **single** budget impact estimate but rather a range and it is this range that the model is designed to produce. Proper design of the analytic framework is a crucial step in BIA.

This section provides an overview of the important components of the analytic framework for BIA.

4.2.1 Perspective

Recommendation:

BIA should be undertaken from the perspective of the budget holder.

Perspective refers to the point of view that will guide the analyst in making choices regarding the elements of the analytic framework and inputs. To be useful, the BIA must be conducted from the perspective of the SHI or other relevant budget holder. Any expenses incurred or savings achieved outside of that are not included.

4.2.2 Scenarios

Recommendation:

BIA should compare scenarios of care, not individual health technologies.

A BIA compares scenarios of care, each defined by a set of health technologies, rather than specific individual technologies [57]. At least two scenarios must be considered [57]. One is the reference scenario defined as the current mix of health technologies and the other is the forecasted new mix of health technologies.

4.2.3 Population

Recommendation:

The likely number of insured citizens using the health technology should be forecast.

The size of the covered population is one of the key factors that determines the amount of the budget that will be spent on the new health technology. To the number of potential users, the forecast uptake of the health technology is applied to yield the projected number of actual users. Any expected off-label use of the new health technology should not be included in the main budget impact analysis, but may be considered in sensitivity analyses [58]. In predicting

the rate of adoption, both substitution of existing health technologies and induced demand need to be considered.

4.2.4   Time Horizon

Recommendation:

The time horizon should be relevant to the budget holder.

The budget impact should be presented for time horizons that are of most relevance to the budget holder in view of their budgeting process [57]. These are usually short term. Since the impact on the budgets is likely to change over time after the new health technology is introduced — both because of gradual market adoption and longer term effects on the condition of interest — these should be estimated and presented for at least two budget cycles [59]. To be useful, the output must thus be the period-by-period level of expenses and savings rather than a single "net present value" [57]. Thus, no discounting of the financial streams is applied.

4.2.5   Other Factors

Recommendations:

- **The model should allow for relevant subgroups of the population to be considered.**

- **Costs should be estimated according to the methods outlined in Section 3.**

- **Results should be presented as a range rather than a single point estimate.**

- **Results should be presented both in terms of the total budget impact and as a fraction of the annual budget.**

References

1. Gesetz zur Stärkung des Wettbewerbs in der Gesetzlichen Krankenversicherung (GKV-Wettbewerbsstärkungsgesetz - GKV-WSG). 26.03.2007. Bundesgesetzblatt 2007; Teil 1(11): 378-473.

2. Graf von der Schulenburg JM, Greiner W, Jost F, Klusen N, Kubin M, Leidl R et al. Deutsche Empfehlungen zur gesundheitsökonomischen Evaluation: dritte und aktualisierte Fassung des Hannoveraner Konsens. Gesundheitsökonomie & Qualitätsmanagement 2007; 12(5): 285-290.

3. Antes G, Jöckel KH, Kohlmann T, Raspe H, Wasem J. Kommentierende Synopse der Fachpositionen zur Kosten-Nutzenbewertung für Arzneimittel: erstellt im Auftrag des Bundesministeriums für Gesundheit [Online]. 10.2007 [last access 25.08.2008]. URL: http://pdf.bmgs.comspace.de/bmgs/temp/pse2ctemplateId3draw2cproperty3dpublicationFile2 epdf2fkommentierte2dsynopse2epdf/index/start.htm.

4. Bundesministerium für Gesundheit. Ergebnis der wissenschaftlichen Klausurtagung zur Einführung einer Kosten-Nutzenbewertung für Arzneimittel in Deutschland am 7. und 8. November 2007 [Online]. 11.2007 [last access 25.08.2008]. URL: http://pdf.bmgs.comspace.de/bmgs/temp/emplateId3draw2cproperty3dpublicationFile2epdf2f ergebniswiss2dklausurtagung2epdf/index/start.htm.

5. Jöckel KH, Kohlmann T, Raspe H, Wasem J. Zentrale Schlussfolgerungen der Kommentierenden Synopse der Fachpositionen zur Kosten-Nutzen-Bewertung für Arzneimittel unter Berücksichtigung der Ergebnisse der Fachtagung am 18. Juni 2007 und der wissenschaftlichen Klausurtagung am 7./8. November 2007 [Online]. 20.12.2007 [last access 25.08.2008]. URL: http://pdf.bmgs.comspace.de/bmgs/temp/mplateId3draw2cproperty3dpublicationFile2epdf2fz entrale2dschulssfolgerungen2epdf/index/start.htm.

6. Gold MR, Russell LB, Siegel JE (Ed). Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.

7. ISPOR. Building a Pragmatic Road: An ISPOR Development Workshop on Moving the QALY Forward [Online]. 2008 [last access 08.10.2008].URL: http://www.ispor.org/meetings/MeetingsInvited.aspx.

8. Soanes C, Hawker S. Compact Oxford English dictionary of current English. Oxford: Oxford University Press; 2005.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Methoden: Version 3.0 [Online]. 27.05.2008 [last access 25.08.2008]. URL: http://www.iqwig.de/download/IQWiG_Methoden_Version_3_0.pdf.

10. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: the index of ADL; a standardized measure of biological and psychosocial function. JAMA 1963; 185(12): 914-919.

11. Torrance GW, Drummond MF, Walker V. Switching therapy in health economics trials: confronting the confusion. Med Decis Making 2003; 23(4): 335-340.

12. Gardiner P, Edwards W. Public values: multiattribute utility measurement for social decision making. In: Kaplan MF, Schwartz S (Ed). Human judgment and decision processes. New York: Academic Press; 1975. p. 1-38.

13. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilites Index (HUI): concepts, measurement properties and applications. Health Qual Life Outcomes [Online] 2003; 1: 54. URL: http://www.hqlo.com/content/pdf/1477-7525-1-54.pdf.

14. Felder-Puig R, Frey E, Sonnleithner G, Feeny D, Gadner H, Barr RD et al. German cross-cultural adaptation of the Health Utilities Index and its application to a sample of childhood cancer survivors. Eur J Pediatr 2000; 159(4): 283-288.

15. Rabin R, De Charro F. EQ-5D: a measure of health status from the EuroQuol Group. Ann Med 2001; 33(5): 337-343.

16. Greiner W, Claes C, Busschbach JJV, Graf von der Schulenburg JM. Validating the EQ-5D with time trade off for the German population. Eur J Health Econ 2005; 6(2): 124-130.

17. Siebert U. When should decision-analytic modeling be used in the economic evaluation of health care? Eur J Health Econ 2003; 4(3): 143-150.

18. Eriksen S, Keller LR. A multiattribute-utility-function approach to weighing the risks and benefits of pharmaceutical agents. Med Decis Making 1993; 13(2): 118-125.

19. Farrar JT, Dworkin RH, Mitchell MB. Use of the cumulative proportion of responders analysis graph to present pain data over a range of cut-off points: making clinical trial data more understandable. J Pain Symptom Manage 2006; 31(4): 369-377.

20. Whiteheat WE. Definition of a responder in clinical trials for functional gastrointestinal disorders: report on a symposium. Gut 1999; 45(Suppl II): II78-II79.

21. Burke L, Stifano T. Guidance for industry: patient-reported outcome measures; use in medical product development to support labeling claims; draft guidance. Health Qual Life Outcomes [Online] 2006; 4: 79. URL: http://www.hqlo.com/content/pdf/1477-7525-4-79.pdf.

22. Nord E. Towards cost-value analysis in health care? Health Care Anal 1999; 7(2): 167-175.

23. Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB et al.(Ed). Making choices in health: WHO guide to cost-effectiveness analysis. Genf: World Health Organization; 2003.

24. Cornu C, Boutitie F, Candelise L, Boissel JP, Donnan GA, Hommel M et al. Streptokinase in acute ischemic stroke: an individual patient data meta-analysis; the Thrombolysis in Acute Stroke Pooling Project. Stroke 2000; 31(7): 1555-1560.

25. Kolominsky-Rabas PL, Heuschmann PU, Marschall D, Emmert M, Baltzer N, Neundörfer B et al. Lifetime cost of ischemic stroke in Germany: results and national projections from a population-based stroke registry; the Erlangen Stroke Project. Stroke 2006; 37(5): 1179-1183.

26. Schöffski O, Graf von der Schulenburg JM. Gesundheitsökonomische Evaluationen. Berlin: Springer; 2007.

27. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions: a binary choice analysis. Health Econ 2004; 13(5): 437-452.

28. Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. BMJ 2004; 329(7459): 224-227.

29. Birch S, Gafni A. The biggest bang for the buck or bigger bucks for the bang: the fallacy of the cost-effectiveness threshold. J Health Serv Res Policy 2006; 11(1): 46-51.

30. Caro JJ, O'Brien JA. The costs of venous thromboembolism in the United States. In: Dalen JE (Ed). Venous thromboembolism. New York: Dekker; 2003. p. 331-350. (Lung biology in health and disease; Vol. 180).

31. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2005.

32. Academy of Managed Care Pharmacy, Foundation for Managed Care Pharmacy. The AMCP format for formulary submissions: a format for submission of clinical and economic data in support of formulary consideration by health care systems in the United States; version 2.1 [Online]. 04.2005 [last access 26.08.2008]. URL: http://www.fmcpnet.org/data/resource/Format~Version_2_1~Final_Final.pdf.

33. Hjelmgren J, Berggren F, Andersson F. Health economic guidelines: similarities, differences and some implications. Value Health 2001; 4(3): 225-250.

34. Langley PC. Formulary submission guidelines for Blue Cross and Blue Shield of Colorado and Nevada. Pharmacoeconomics 1999; 16(3): 211-224.

35. Commonwealth Department of Health and Ageing. Guidelines for the pharmaceutical industry on preparation of submissions to the Pharmaceutical Benefits Advisory Committee: including major submissions involving economic analyses. Canberra: DHA; 2002. URL: http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pbs-general-pubs-guidelines-index.htm/$FILE/guidelines.pdf.

36. Finnish Ministry of Social Affairs and Health. Guidelines for preparation of an account of health economic aspects. Helsinki: Ministry of Social Affairs and Health; 1999.

37. Garrattini L, Grilli R, Scopelliti D, Mantovani L. A proposal for Italian guidelines in pharmacoeconomics. Pharmacoeconomics 1995; 7(1): 1-6.

38. Schöffski O, Graf von der Schulenburg JM, Greiner W. Hannover Guidelines für die ökonomische Evaluation von Gesundheitsgütern und -dienstleistungen. In: Braun W, Schaltenbrand R (Ed). Pharmakoökonomie: Methodik, Machbarkeit und Notwendigkeit; Berichtsband zum 1. Symposium. Witten: Universität Witten/Herdecke Verlagsgesellschaft; 1995. p. 185-187.

39. König HH, Barry JC, Leidl R, Zrenner E. Cost-effectiveness of orthoptic screening in kindergarten: a decision-analytic model. Strabismus 2000; 8(2): 79-90.

40. Laux G, Heeg BMS, Van Hout BA, Mehnert A. Cost and effects of long-acting risperidone compared with oral atypical and conventional depot formulations in Germany. Pharmacoeconomics 2005; 23(Suppl 1): 49-61.

41. Roze S, Valentine WJ, Evers T, Palmer AJ. Acarbose in addition to existing treatments in patients with type 2 diabetes: health economic analysis in a German setting. Curr Med Res Opin 2006; 22(7): 1415-1424.

42. Schiefke I, Rogalski C, Zabel-Langhennig A, Witzigmann H, Mössner J, Hasenclever D et al. Are endoscopic antireflux therapies cost-effective compared with laparoscopic fundoplication? Endoscopy 2005; 37(3): 217-222.

43. Gericke CA, Wismar M, Busse R. Cost-sharing in the German health care system [Online]. 2004 [last access 26.08.2008]. URL: http://www.ww.tu-berlin.de/diskussionspapiere/2004/dp04-2004.pdf.

44. Hülsemann JL, Mittendorf T, Merkesdal S, Zeh S, Handelmann S, Graf von der Schulenburg JM et al. Direct costs related to rheumatoid arthritis: the patient perspective. Ann Rheum Dis 2005; 64(10): 1456-1461.

45. Spottke AE, Reuter M, Machat O, Bornschein B, Von Campenhausen S, Berger K et al. Cost of illness and its predictors for Parkinson's disease in Germany. Pharmacoeconomics 2005; 23(8): 817-836.

46. Busse R, Stargardt T, Schreyögg J, Simon C, Martin M. Defining benefit catalogues and entitlements to health care in Germany: decision makers, decision criteria and taxonomy of catalogues [Online]. 2005 [last access 26.08.2008]. URL: http://www.ww.tu-berlin.de/diskussionspapiere/2005/dp05-2005.pdf.

47. Brouwer WBF, Koopmanschap MA, Rutten FFH. Productivity costs measurement through quality of life: a response to the recommendation of the Washington Panel. Health Econ 1997; 6(3): 253-259.

48. O'Brien JA. Cost estimation: finding and extracting cost data. In: ISPOR 12th Annual International Meeting; 19.-23.05.2007; Arlington, USA.

49. Sander B, Bergemann R. Economic burden of obesity and its complications in Germany. Eur J Health Econ 2003; 4(4): 248-253.

50. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. J Health Serv Res Policy 2004; 9(2): 110-118.

51. National Institute for Clinical Excellence. Guide to the methods of technology appraisal. London: NICE; 2004. URL: http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf.

52. Collège des Économistes de la Santé. French guidelines for the economic evaluation of health care technologies [Online]. 09.2004 [last access 26.08.2008]. URL: http://www.ces-asso.org/docs/France_Guidelines_HE_Evaluation.PDF.

53. Netten A. Costs, prices and charges. In: Netten A, Beecham J (Ed). Costing community care: theory and practice. Aldershot: Avebury; 1993. p. 87-103.

54. Schreyögg J, Tiemann O, Busse R. Cost accounting to determine prices: how well do prices reflect costs in the German DRG-system? Health Care Manag Sci 2006; 9(3): 269-279.

55. Nguyen-Kim L, Zeynep O, Paris V, Semet C. The politics of drug reimbursement in England, France and Germany. Paris: IRDES; 2005. (Issues in health economics; Vol. 99). URL: http://www.irdes.fr/EspaceAnglais/Publications/IrdesPublications/QES099.pdf.

56. Trueman P, Drummond M, Hutton J. Developing guidance for budget impact analysis. Pharmacoeconomics 2001; 19(6): 609-621.

57. Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices; budget impact analysis. Value Health 2007; 10(5): 336-347.

58. Orlewska E, Mierzejewski P. Proposal of Polish guidelines for conducting financial analysis and their comparison to existing guidance on budget impact in other countries. Value Health 2004; 7(1): 1-10.

59. Mauskopf JA, Earnshaw S, Mullins CD. Budget impact analysis: review of the state of the art. Expert Review of Pharmacoeconomics and Outcomes Research 2005; 5(1): 65-79.