IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Institute for Quality and Efficiency in Health Care

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

For Consultation

Version 1.0

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This Report on the proposed Methods is the result of a process of consultation with an International Expert Panel. 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
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This is a working document. IQWiG is publishing this Methods for consultation. An operational version of the Methods for Assessment of the Relation of Benefits to Costs in the German Statutory Health Care System will be published after consultation. Discussion of the Methods is explicitly desired in order to achieve continuous improvement.

Preamble

With the introduction of the health care reform in 2004 (Health Care Modernisation Act; *Gesundheits-Modernisierungsgesetz, GMG*), legislation determined the establishment of a new Institute, independent of the state, 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 legislative 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 assess 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 superior 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 Spitzenverband Bund der Krankenkassen (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 superior 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 Spitzenverband Bund der Krankenkassen 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.

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, even if the comparisons are still typically done within a single therapeutic area. This inevitably involves judgments about the worthiness of one disease versus another and of benefits relative to each other (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 treatments in each therapeutic area without tackling the broader issue of prioritizing across the health care system. Thus, the evaluation focuses on ensuring that there is efficiency in managing each 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 Spitzenverband Bund der Krankenkassen 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 the cost of supplies purchased by patients, 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.

[1] For example such as Quality-Adjusted Life Year (QALY)

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 estimated 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 should therefore be regarded as a guideline when evaluating the efficiency of a medical intervention. 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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SECTION 1

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. Although these sound and consistent evaluations of all relevant data 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 the 1st of 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 recognised standards of evidence-based medicine. The economic evaluation has to be conducted according to the relevant internationally recognised standards, particularly in health economics.

1.1.1 Selection of Experts

In compliance with the requirements set by law, IQWiG established an international expert panel 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 the 9th of 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 will be completed after the Methods document is final at the end of the Consultation process.

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 October 15th 2007 and a final draft version of the Methods was sent to the IQWiG Scientific Advisory Board and to the IQWiG Methods Group on October 22nd 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]. Remaining points were referred to settlement in the final version after public consultation.

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. After the completion of the consultation process, technical papers which cover details of the Efficiency Frontier, Cost Estimation, Modeling and additional aspects of Budget Impact Analysis will be produced.

This 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 (other approaches will be considered in the technical supplement) are universally accepted and, thus, are not able to form the basis for ceiling price assessments in Germany. Thus, a modified approach is required. 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 existing standards 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 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"[6]. 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 efficiency frontier concept was chosen as the framework for IQWiG assessment of health technologies because it meets the requirements imposed by German law while remaining consistent with basic international methodological standards. 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.

2.2.2 Definition

A basic requirement in comparative economic evaluation is that there is efficiency in the current mix of health technologies [7]. In other words, the assessment of a new therapy takes as a point of departure that the existing health technologies all deserve to be used because, in combination, they provide the most value for the allocated budget. If this were not so, then any sensible decision-maker would seek to optimize the existing mix before considering any new intervention; and proponents of a new agent could focus on the "weakest' of the current ones to show a comparative advantage that might, nevertheless, not improve the overall efficiency of resource use.

This efficient mix of health technologies is known as the "efficiency frontier" because it represents the best that the system can do with available interventions: any that are not at the frontier should not be part of the mix as they are less desirable because they produce the same

or less value at a higher cost than other existing treatments, singly or in combination[2]. By the same token, the region "above" the frontier identifies an area of potential interventions that would be better than existing ones because they would provide equal or more value at less or equivalent cost (Figure 2-1). Should they become available, the system would have to adjust the mix to incorporate them because the resulting combination of therapies would deliver more with available resources.

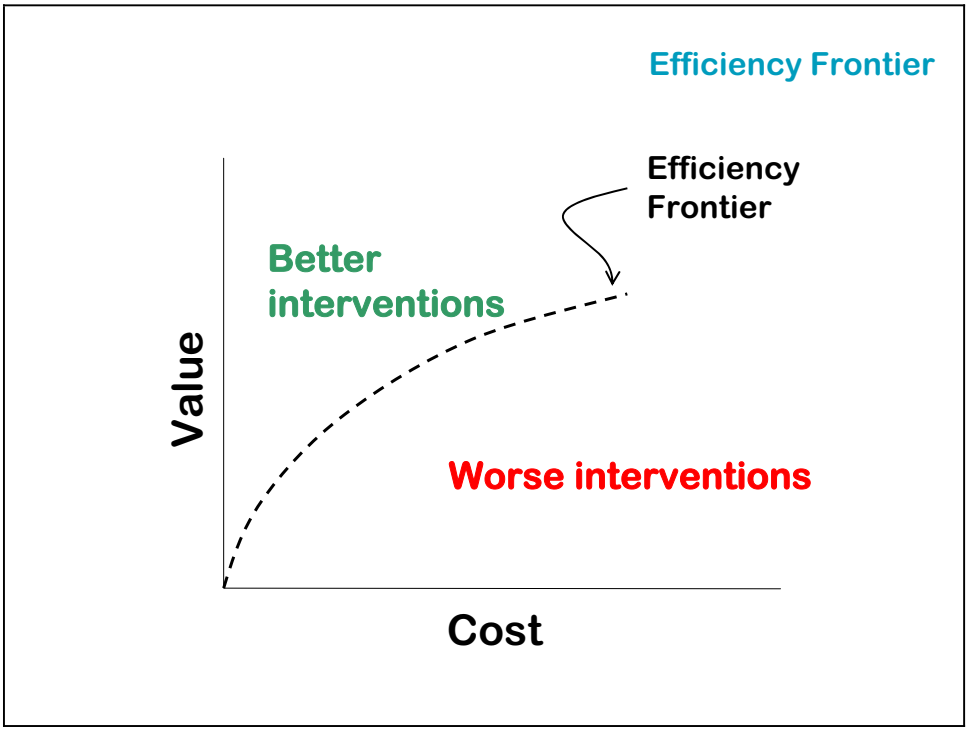

Figure 2-1 **Basic concept of the efficiency frontier.** It compares the value produced with the cost of doing so. Above the frontier is a zone of new interventions that are better than the existing ones in that particular therapeutic class because they produce more value for a given cost; while less efficient ones lie below it.

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

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

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.

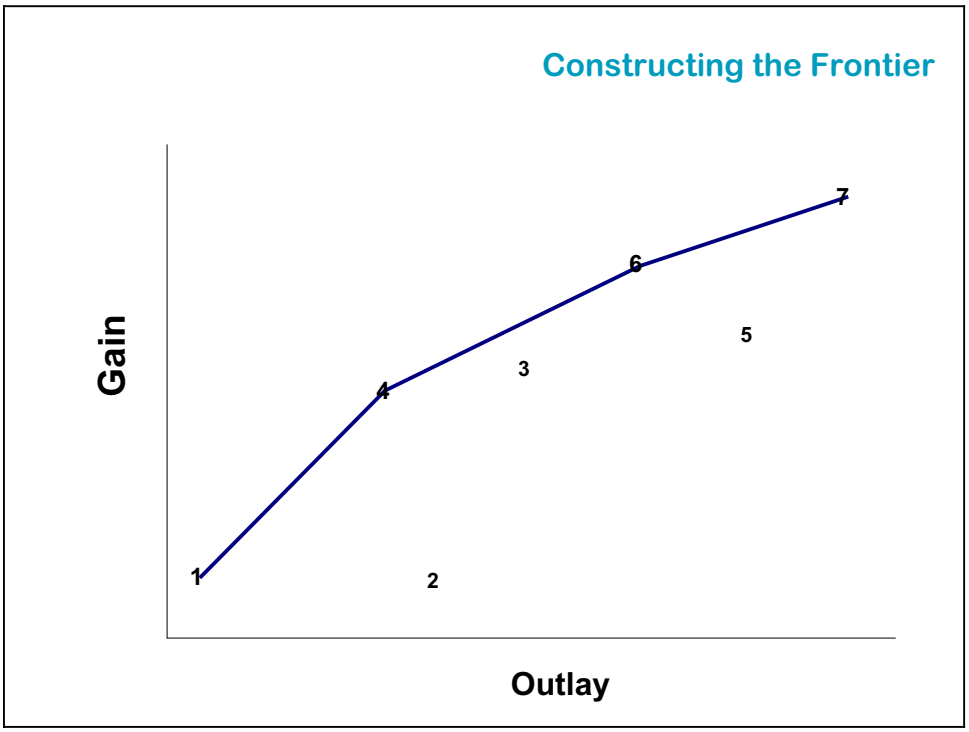

Figure 2-2 **Construction of the theoretical efficiency frontier** by plotting the seven available health technologies according to their required outlays and the gains they provide. The line segments identifying the health technologies with the highest gains for successively higher outlays form the 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).

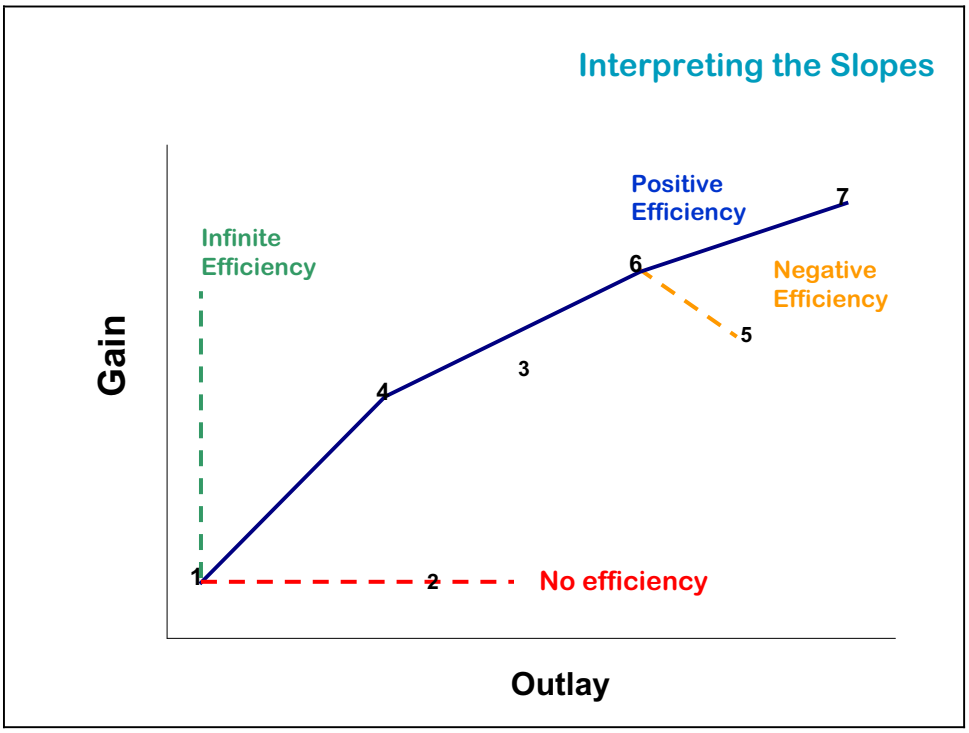

Figure 2-3 **Interpreting the slopes given by the theoretical efficiency frontier.** The horizontal slope indicates no efficiency (e.g., 2 versus 1) while the vertical slope indicates infinite efficiency. Positive slopes (e.g., between points 6 and 7) reflect additional gains for increased cost while 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[3]. 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.

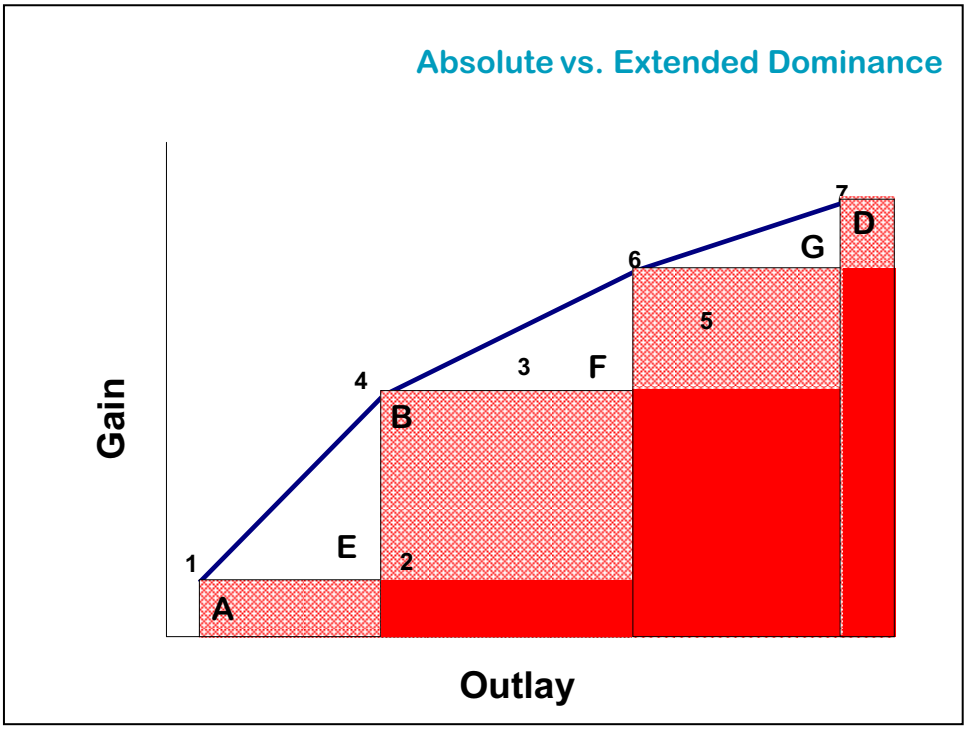

Figure 2-4 **Absolute versus extended dominance.** The theoretical efficiency frontier (solid line) joins those points that are not inefficient relative to any other option nor combination of options. These options demarcate rectangles A-D and any options in those areas (e.g., 2, 5) are clearly inefficient. 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

[3] Except for the dominated rectangle (B) created by option 3, as discussed further on.

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.

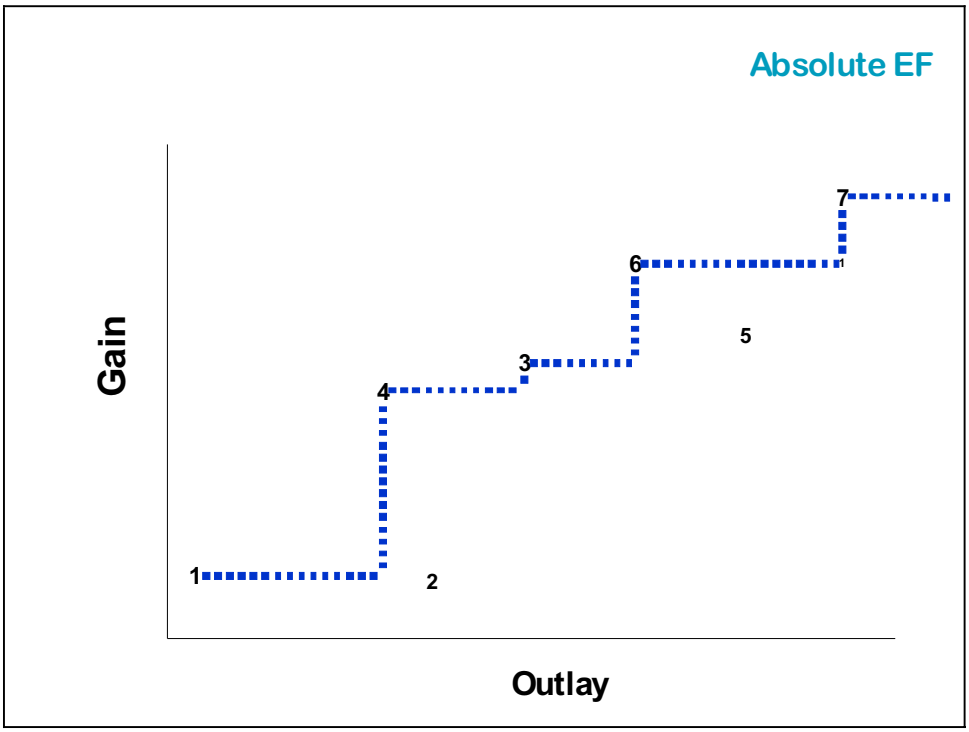

Figure 2-5 **Absolute efficiency frontier** given by the staircase incorporating an option (3) that is not clearly inefficient relative to the existing ones.

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).

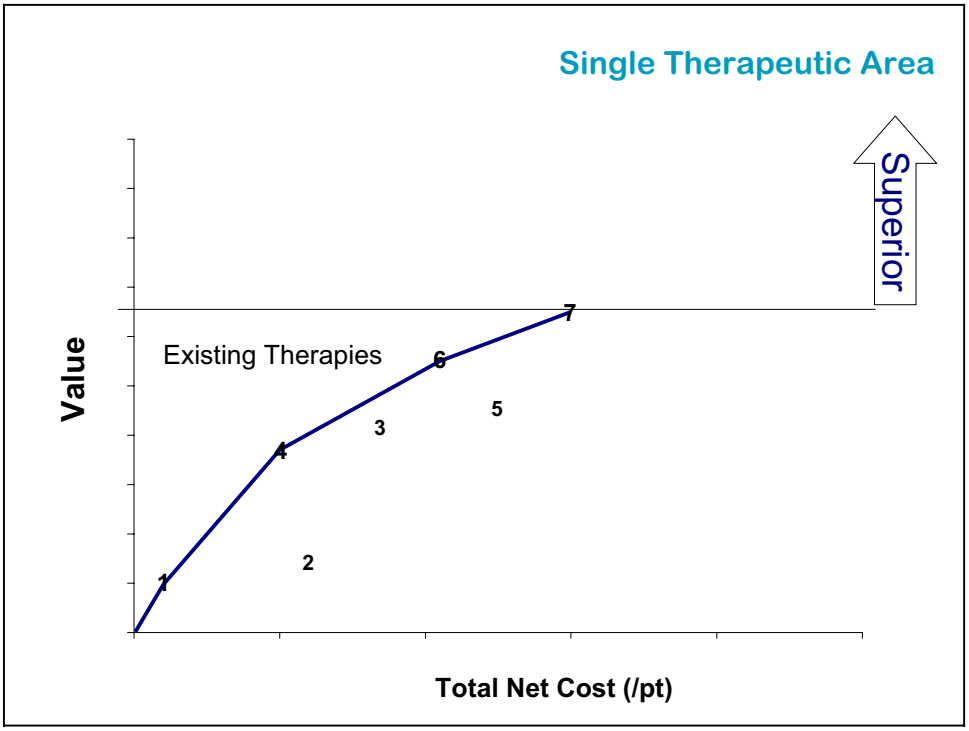

Figure 2-6 **Theoretical efficiency frontier modified for use in Germany in the context of a single therapeutic area.** The plotted numbers reflect the therapies that IQWiG has selected as appropriate comparators. (In reality, many of these therapies, especially 1 and 2, might not be evaluated because 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[4]**
- **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 of the new 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

[4] 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 [8], and the approach to quantifying the cost inputs in Section 3.

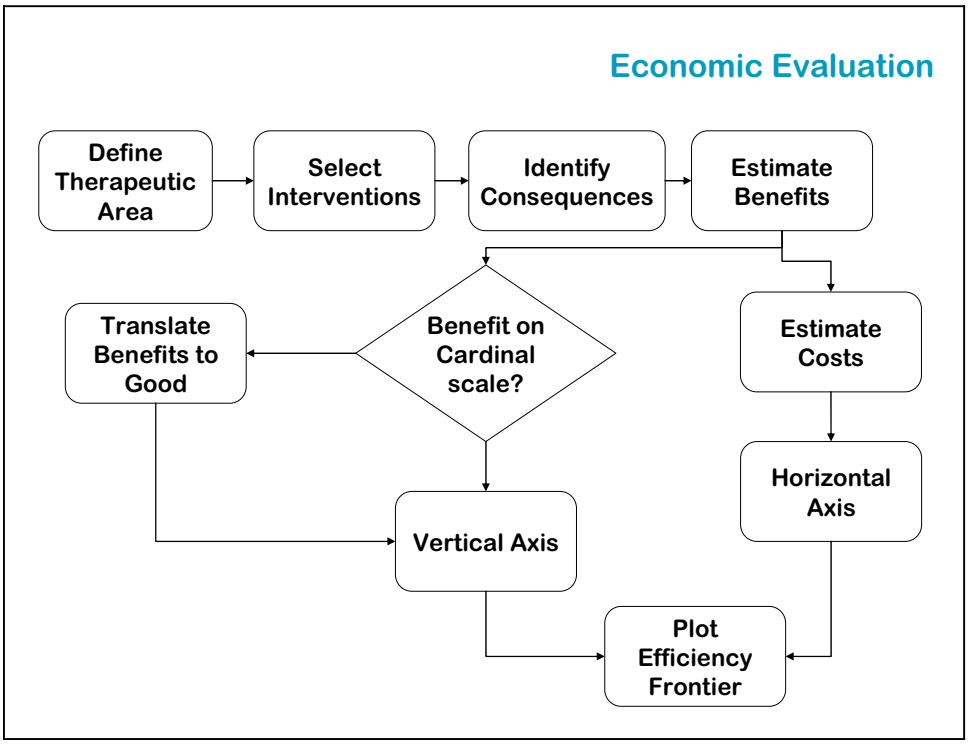

Figure 2-7 Proposed process of economic evaluation.

2.3.1 Vertical Axis

Recommendations:

- **The vertical axis should reflect the health benefits assessed by IQWiG.**
- **The benefits should be parameterized in terms of the actual clinical measures (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 modeling to address the (longer) time horizon required for economic analysis and proper 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 (others will be provided in the technical supplement).

2.3.1.1 Translating the Benefit for Economic Evaluation

IQWiG carries out the evaluation of benefit according to its published Methods {Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2006 98 /id}. IQWiG reaches one of five determinations for each predefined patient-relevant endpoint:

1) Evidence of a benefit (harm) exists.

2) Indications are available that a benefit (harm) exists.

3) No benefit (harm) exists.

4) Indications are available that no benefit (harm) exists.

5) No evidence and no indication of a benefit (harm) exists.

Determinations 1) and 3) require scientific evidence of an effect or lack thereof; 2) and 4) imply that there is some suggestion of an effect or lack thereof, but the data are inconsistent or insufficient. In the absence of a signal because of insufficient data, IQWiG makes determination 5). For the economic evaluation, only interventions achieving determination 1), and possibly 2), where the beneficial effect outweighs the harms and is superior to that of the comparators would be selected for evaluation.

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

1) The benefit potential, and

2) 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 [9], 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 [10], or the application of so called Multi Attribute Utility Instruments [11] like the Health Utilities Index [12,13] or health status scoring systems like the EQ-5D [14,15]. 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 clinical measures of benefit to a cardinal scale that can be plotted on the vertical axis, it may be necessary to use modeling [16] These techniques can provide for detailed and full estimation of the intervention’s implications for patient’s prognosis. 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 per 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 modeling.

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.

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, one may not know if altering it exogenously will yield the same effect as if the resulting value were obtained naturally.

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.

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 [17]. Such *responder* definitions already exist for many illnesses and are even used as primary endpoints in clinical trials [18,19]. 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 [20]. 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 [21], where society in valuing health programs is assumed not to want to discriminate strongly between programs for patients with different potentials for health – as long as the programs 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 '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 supplement) but it can also be argued that the differential timing can be incorporated directly in assessing how valuable the benefit is [22] . Either way, the approach must be fully justified.

2.3.2 Horizontal Axis

Recommendations:

- **Total net costs per patient should be plotted[5] 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[6].**
- **The costs should be the actual ones that are expected to accrue.**

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

[5] It can also be tabulated

[6] 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.

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 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 only those items covered by SHI. Strict application of this principle could lead, however, to shifting of costs from the covered side to the privately paid side, introducing a distortion in the evaluation. Thus, if there are substantial costs that are borne privately by insured patients and their families, these should also be included. This is especially important if pricing decisions will produce a shift that exceeds this threshold.

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, particularly theoretical ones such as an ill-defined "society".

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 program, 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

[23] 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 [24].

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).

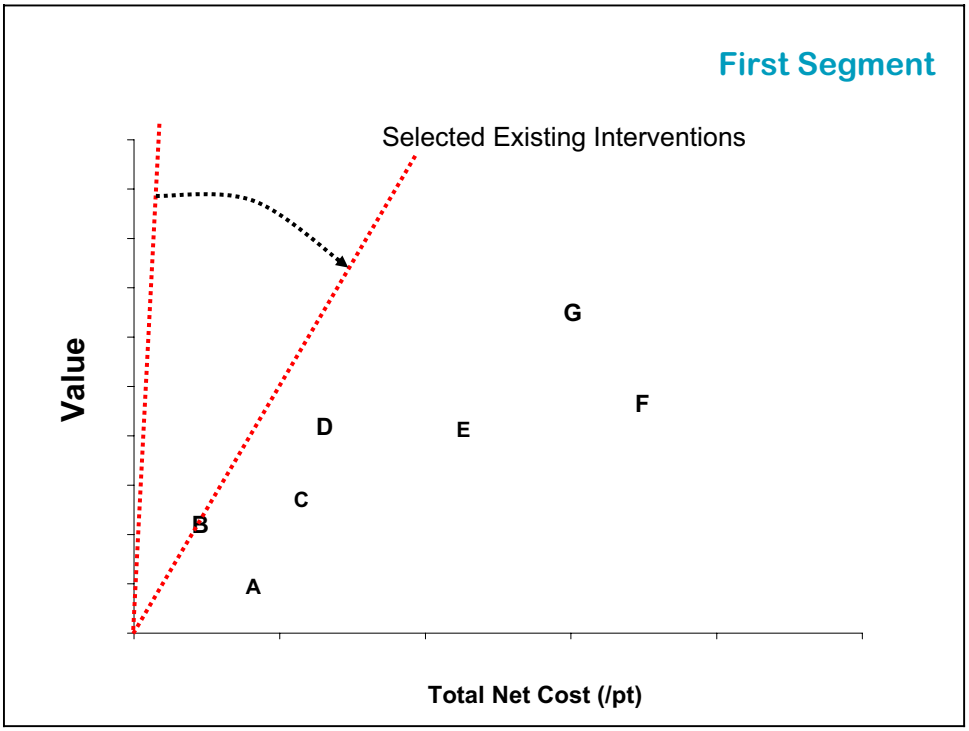

Figure 2-8 **Selecting the first point on the theoretical efficiency frontier**. The figure illustrates the clockwise sweeping of a radius from the vertical axis until it hits a plotted intervention, which is then the first point on the theoretical efficiency frontier. Intervention A is now definitely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

The no intervention point also requires some assessment. Although, by default, it may be taken to be the origin (zero benefit and zero cost), this is not necessarily the case as the absence of intervention may still produce costs due to the untreated illness, monitoring and so on. This can be taken into account (as well as any negative health effects of not intervening) by shifting the axes so that no intervention is at the origin (Figure 2-9). This simply involves taking out the no-intervention amounts from the benefits and costs of the selected health technologies.

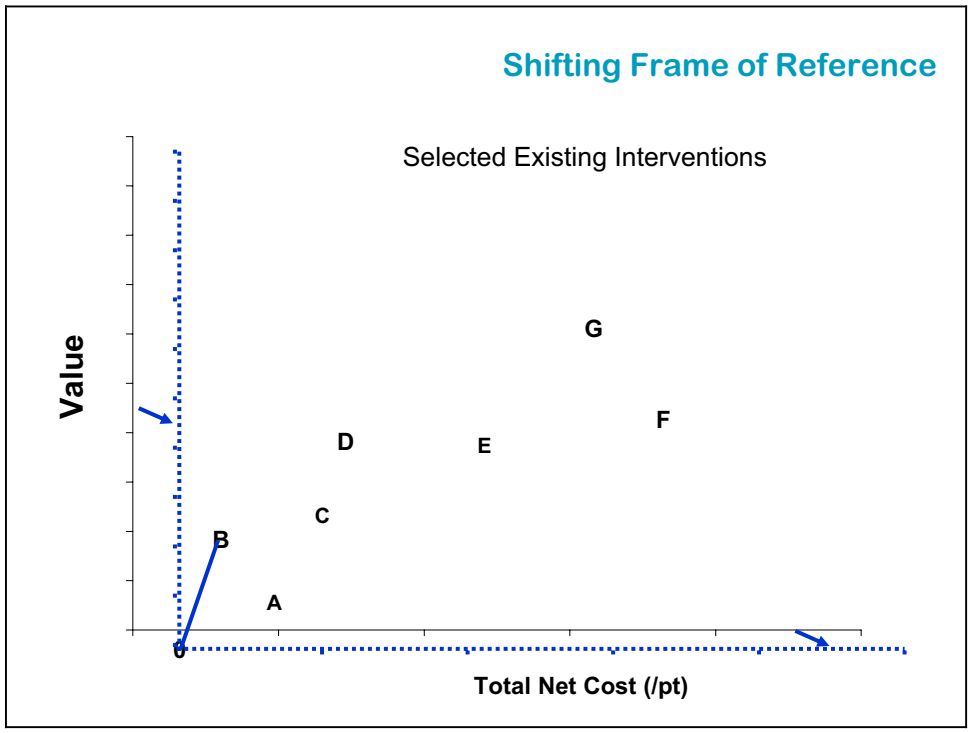

Figure 2-9 **Shifting of the coordinate system** to address a no-intervention point that accrues costs and has negative health effects. The first segment of the theoretical efficiency frontier is then drawn from this new origin to the first intervention identified by the clockwise sweeping radius.

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).

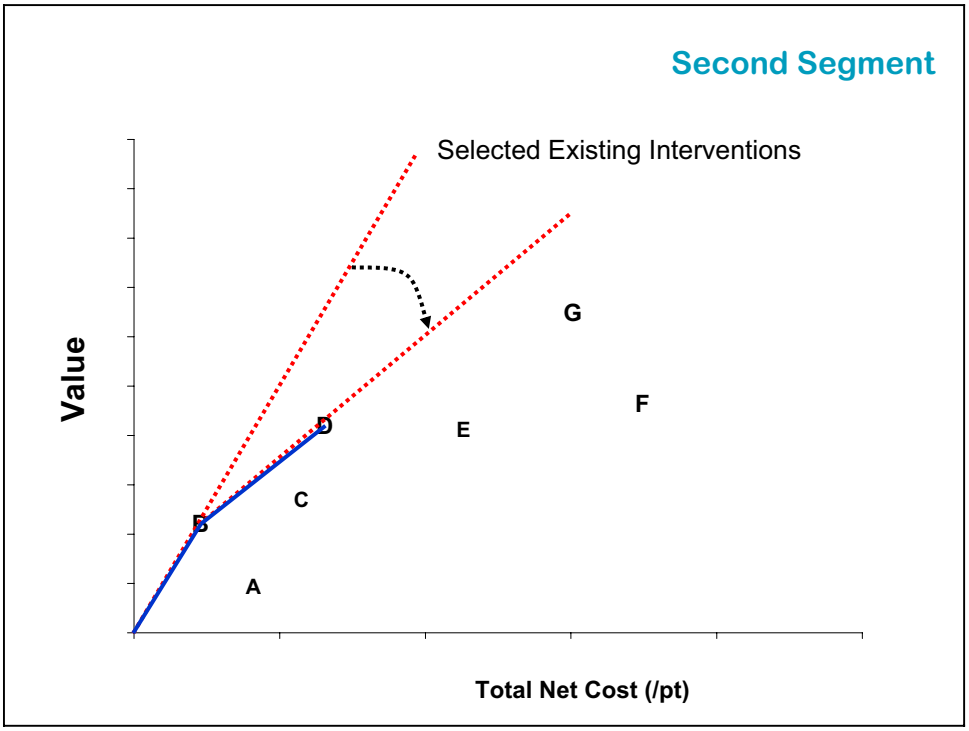

Figure 2-10 Continuing to build the theoretical efficiency frontier by resuming the clockwise sweep of the radius until it hits another intervention; and drawing the next segment between the first intervention identified and this one. Note, intervention C is now also eliminated in theory as any combination 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).

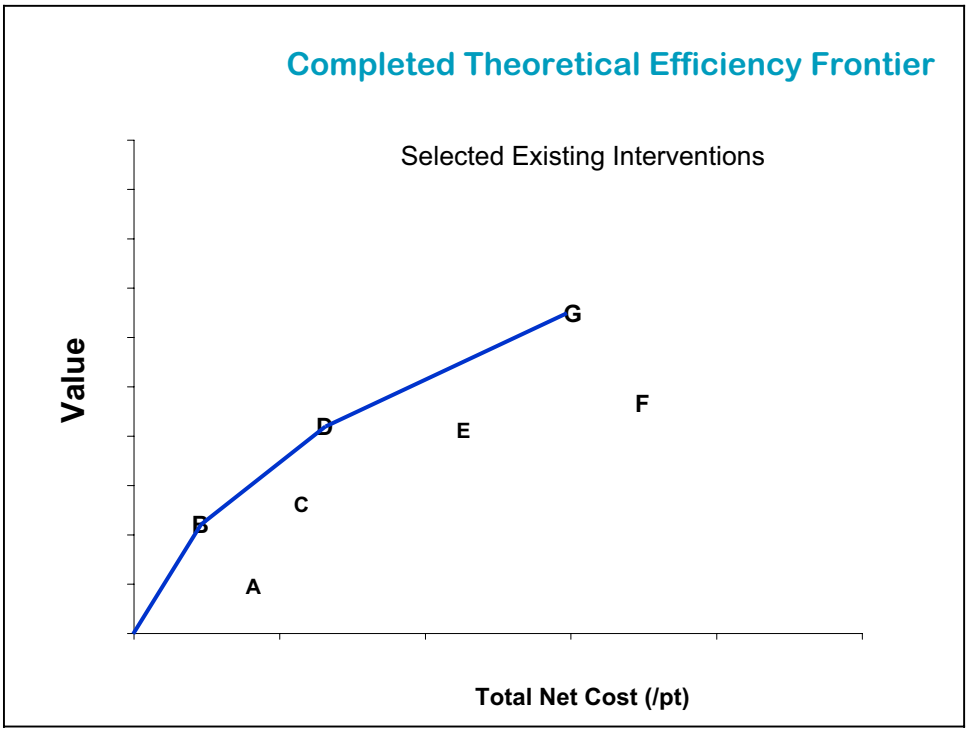

Figure 2-11 Completed theoretical efficiency frontier. The continuing clockwise sweep of the radius hits intervention G next and the segment between D and G is drawn. No other health technologies are part of the frontier because all remaining ones (F) have lower benefits.

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).

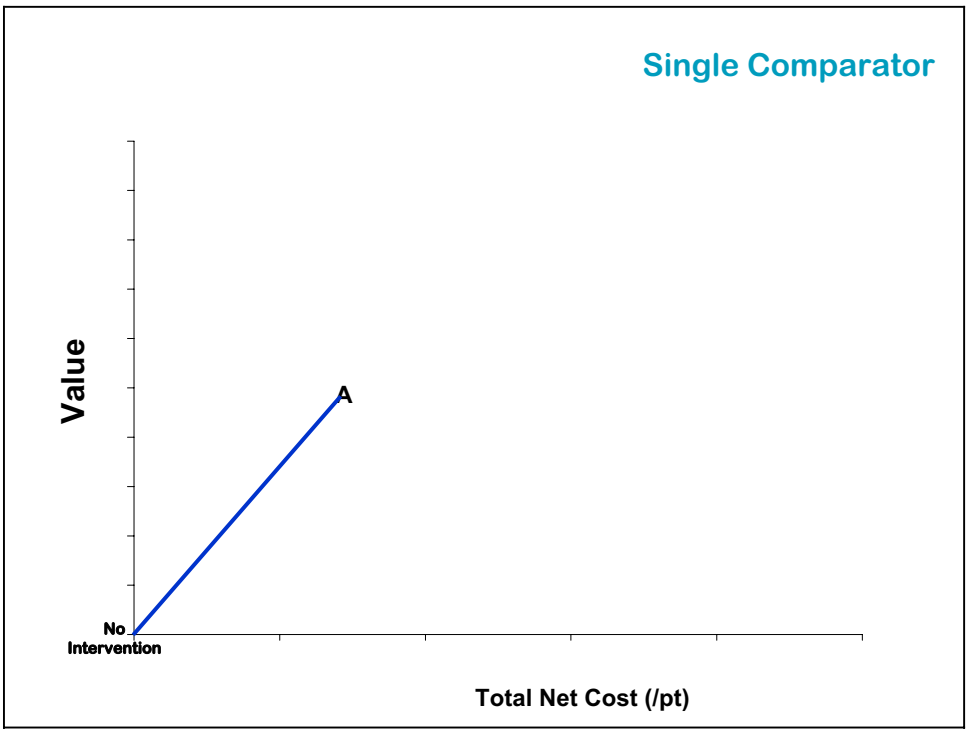

Figure 2-12 Efficiency frontier with a single available comparator, with the frame of reference re-centered on No Intervention.

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 analyzed price, then all subsequent therapies will be judged against its slope with respect to no intervention (see preceding section).

2.4 Decision 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 framework itself provides guidance. In such a two-dimensional framework, particularly when each dimension is quantified in its own units, there can be no clear decision rule. If both the costs and the amount of value produced increase, 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, new intervention. This judgment 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 the technical supplement will address the quantification of uncertainty.

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 [25]. 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 [7].

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 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.

[7] 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[8]. 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. Presumably, only new health technologies that are above the line will be the subject of economic evaluations (but the Method is fully applicable below the line as will be addressed in the technical supplement).

[8] 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)

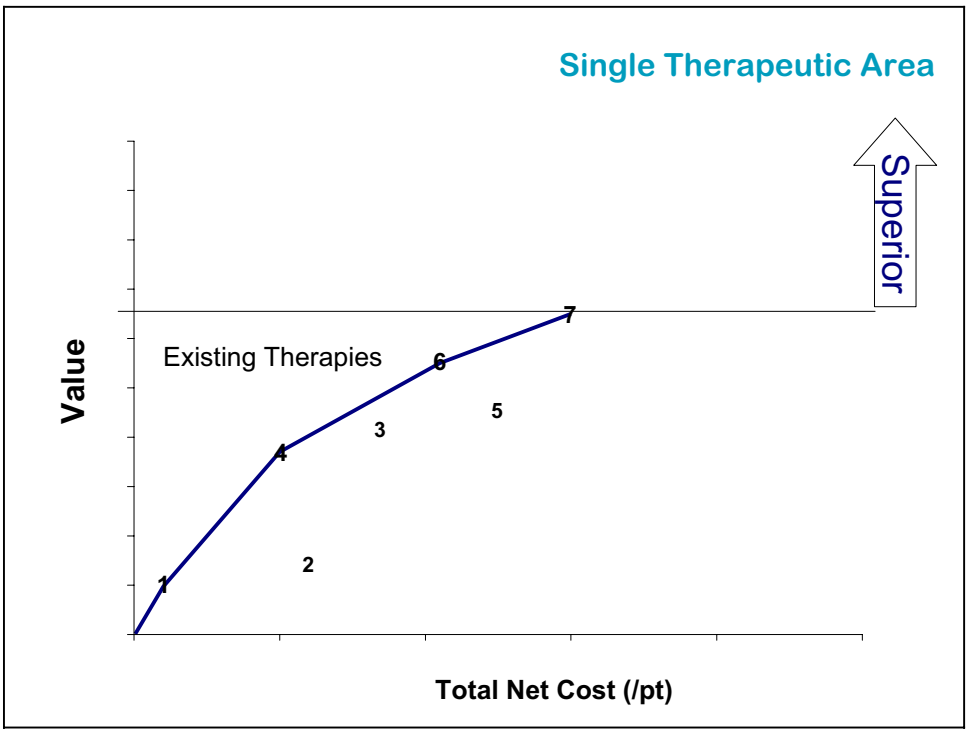

Figure 2-13 Establishing the superiority boundary.

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[9].

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).

[9] Usually, this will also be the one with the superior benefit, but not necessarily if the system is operating inefficiently.

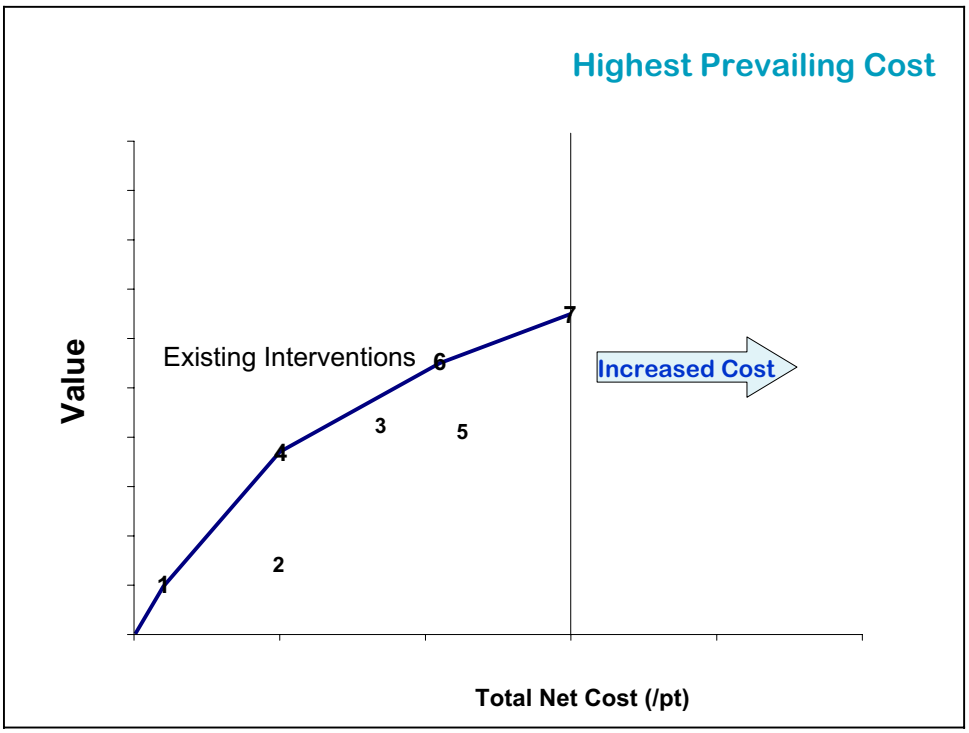

Figure 2-14 Establishing the highest prevailing cost.

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:**

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

    - **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

- **in between, the prevailing pricing may be the appropriate ceiling price but it must be confirmed that it reflects what is reasonable from the point of view of the insured German citizens.**

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).

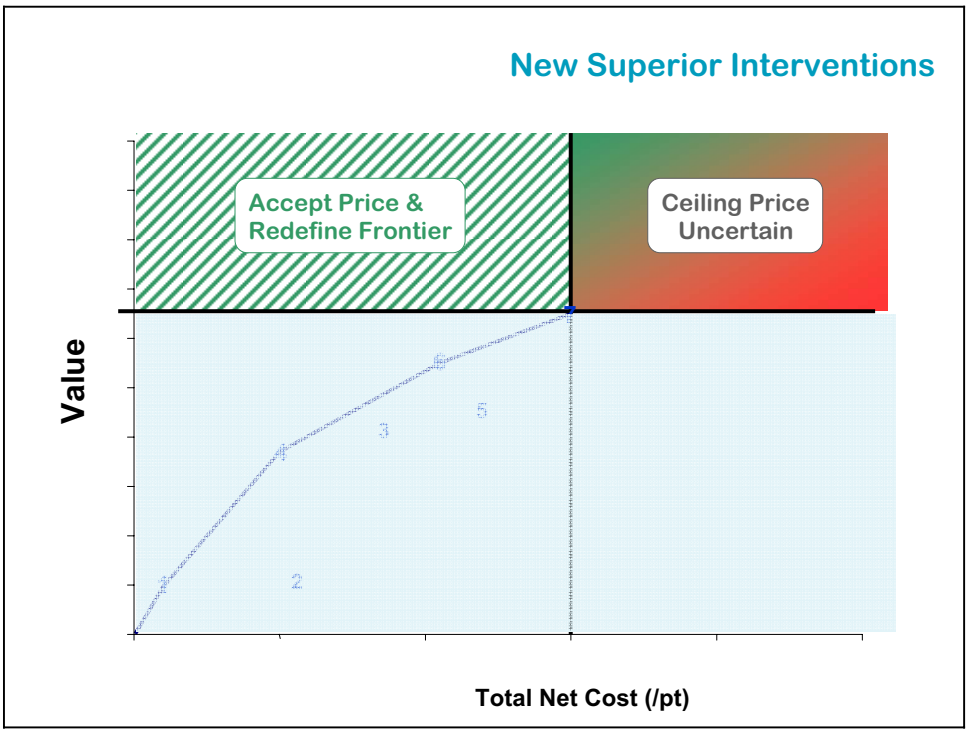

Figure 2-15 Decision zones above the superiority boundary.

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).

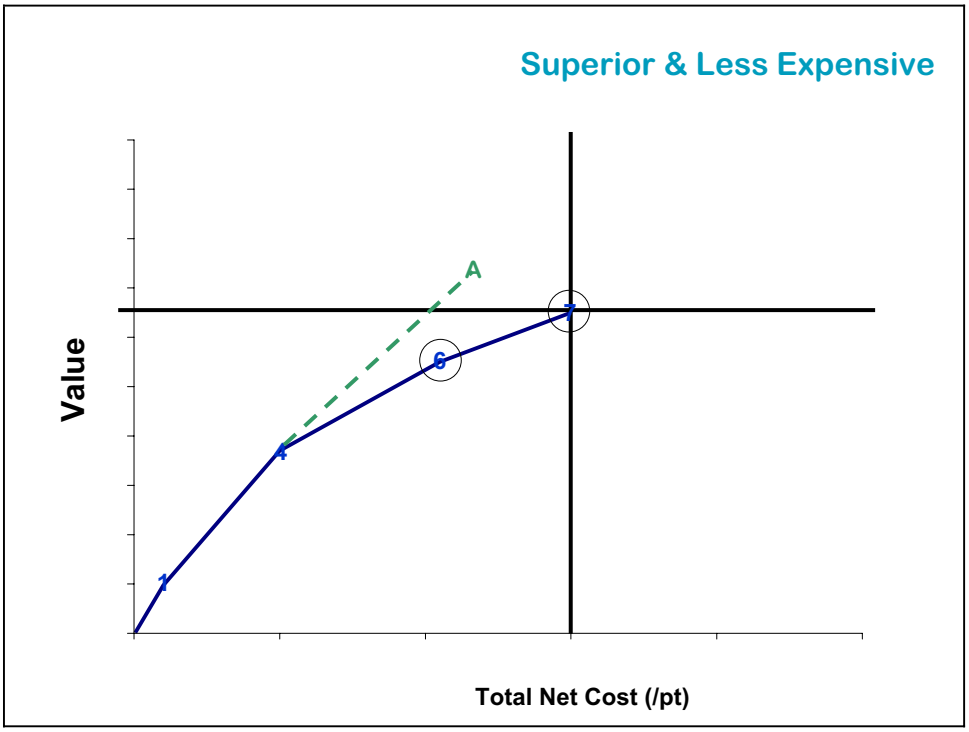

Figure 2-16 **Superior therapy** "A" has a lower total cost than the highest prevailing one and redefines the theoretical efficiency frontier, putting prices of the circled therapies in question.

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 exceed 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).

Clearly, then, there cannot be a firm decision rule for health technologies in this zone. 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[10]. 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 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 decision 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.

[10] 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.

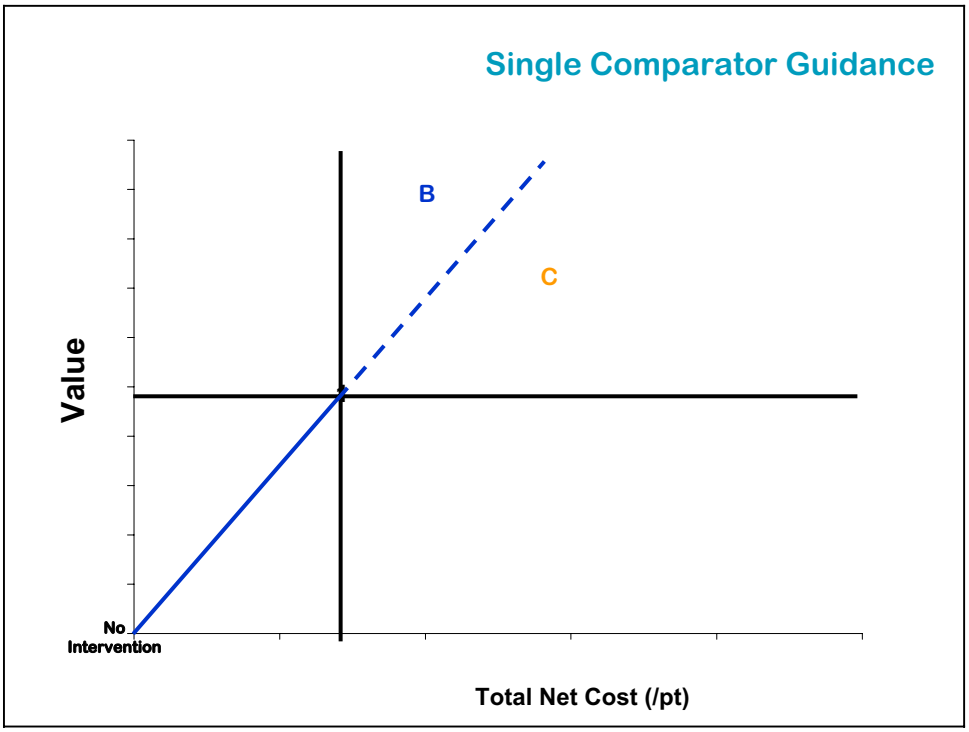

Figure 2-17 **Developing guidance** for new health technologies that both provide more value and are more costly than a single existing intervention in a particular therapeutic area. The dashed extension of the existing efficiency frontier divides the decision zone into a more efficient area (B) and 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. 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.

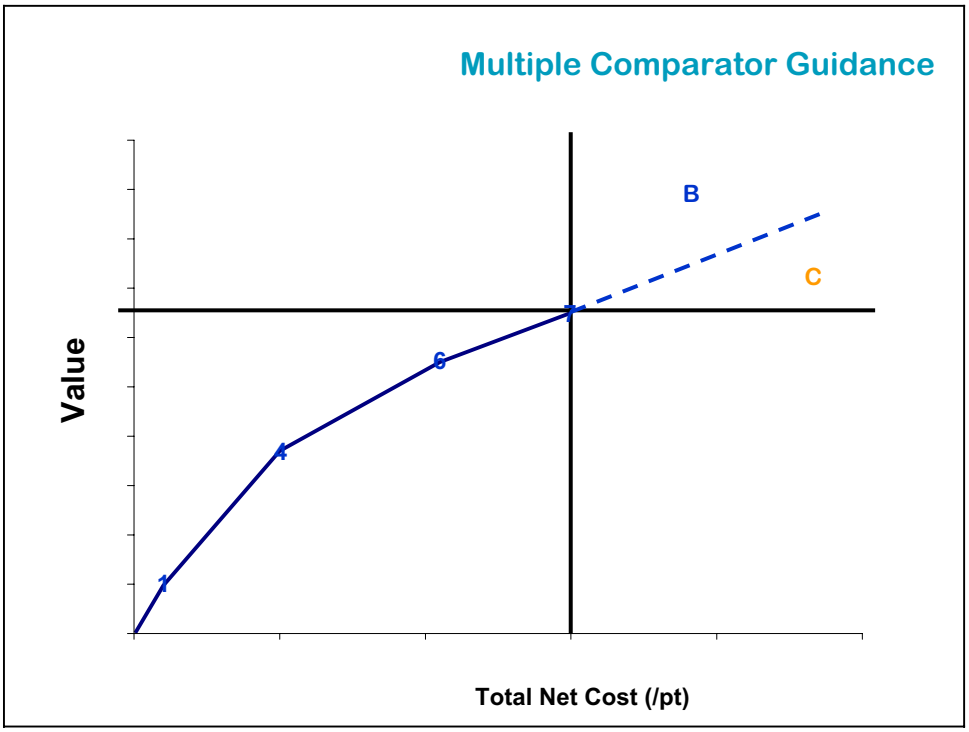

Figure 2-18 **Simple projection of the theoretical efficiency frontier**[11] to provide guidance for assessment of reasonableness of new health technologies that are both more costly and beneficial in a therapeutic area with multiple existing health technologies. The dashed extension of the theoretical efficiency frontier divides the decision zone into an incrementally more efficient area (B) and a less efficient one (C).

Stricter guidance than the simple projection of the theoretical efficiency frontier can be provided by the value-to-cost ratio of the previously superior therapy relative to no intervention (Figure 2-19). This would demarcate a decision zone of clearly better efficiency relative to the least efficient of the existing health technologies that constitute the theoretical efficiency frontier. An even stricter guidance is given by the mean of the existing value-to-cost ratios, indicating zones of greater-than-average efficiency and lower-than average efficiency.

[11] 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.

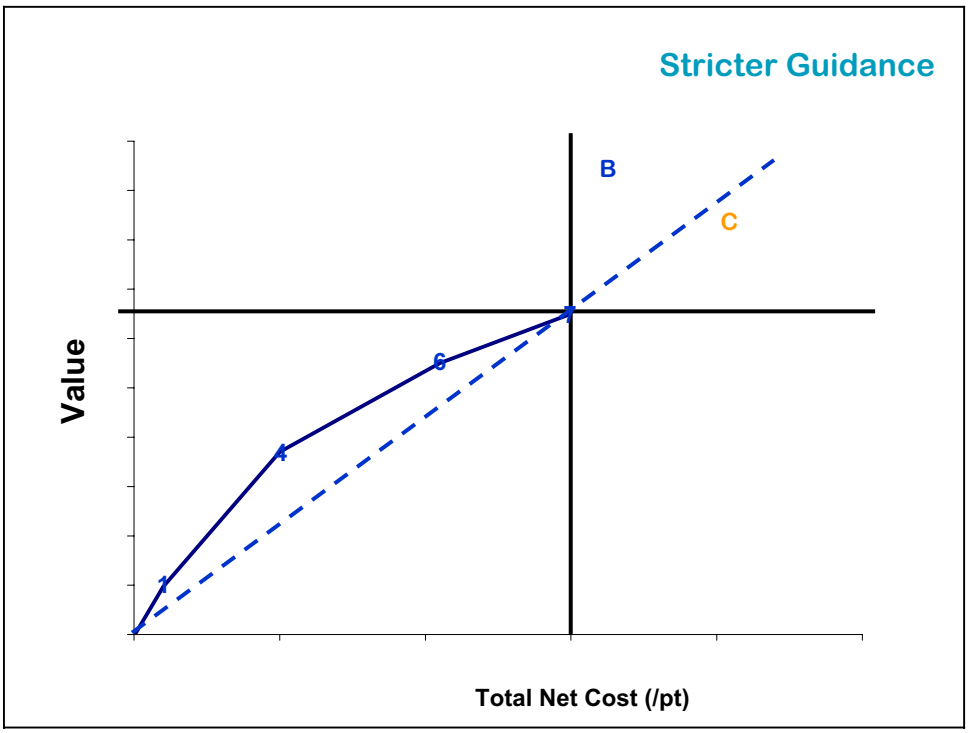

Figure 2-19 **Stricter guidance** for assessment of reasonableness of new health technologies that are both more costly and beneficial in a therapeutic area with multiple existing health technologies. The dashed line reflects the slope between the no intervention point and the existing intervention with the next highest benefit (7). This divides the decision zone into a more efficient area (B) and a less efficient one (C).

Strictest guidance is given by the decision zone bounded by the efficiency of the most efficient intervention on the efficiency frontier (Figure 2-20).

Although these approaches to using the efficiency frontier for setting a ceiling price for a new, superior intervention yield a clear comparison with the existing situation, any one of them should 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 they judge the price of a less efficient intervention reasonable because the added benefit is thought to be worthwhile despite the disproportionate increase in cost.

Alternative approaches to providing guidance can be derived (these will be detailed in the technical supplement). It is not clear what the conceptual foundation would be for these

alternative approaches 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 [26,27]. This has no justification and can lead to poor decisions with no rational basis [28].

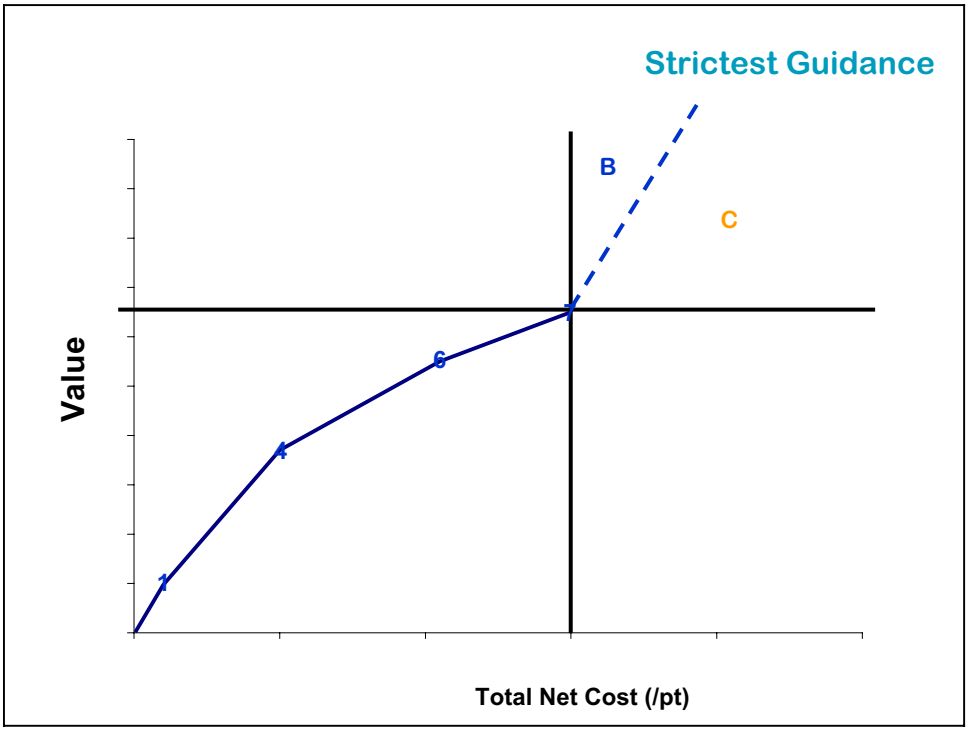

Figure 2-20 **Implementing the strictest guidance** for assessment of reasonableness of new health technologies that are both more costly and beneficial in a therapeutic area with multiple health technologies by using the highest slope of the efficiency frontier (from origin to intervention 1). The dashed line divides the decision zone into a most efficient area (B) and a less efficient (C).

Regardless of the method employed to derive guidance from the existing efficiency frontier for the decision zone involving both higher costs and more value, a consistent approach can be taken to the resulting three possibilities: better efficiency, equivalent efficiency, lower efficiency.

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 (Note, there is also the option of reallocating funding within the area to redistribute resources that are being spent on less efficient health technologies). 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 or other guidance boundary provide additional value at a rate that is no better than that of (some of) the existing health technologies. Thus, they have less to recommend them at the current price than those that are above the projected efficiency frontier and assessing the reasonableness of continuing with the extant price must deal with both their impact on the budget and the desirability of increasing the budget with no gain in efficiency. One option, of course, is to lower the ceiling price, thus placing it on the more desirable side of the guidance boundary.

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 or other guidance boundary pose a problem. Although they provide more value they do so in a much less efficient way than existing health technologies. Thus, accepting to reimburse such a therapy 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 [29]. 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 supplement). Here the focus is on the more practical issues.

Two main types of cost are distinguished in economic evaluations [30]. 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")

Recommendation:

Insured costs should be the main type of expense 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 [31-33]. For example, the Guidelines produced by the Government of Australia [34] 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 [35] and Italy [36]. Even in countries such as Germany, where a broader perspective has been encouraged [2,37], many studies include only insured costs [38-41].

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

Recommendation:

Health care costs not covered by insurance can be included if they are a major component in a particular therapeutic area.

Direct costs not covered by insurance, often referred to as out-of-pocket expenses, are those that are not covered by the third-party payer, such as co-payments, deductibles, over-the-counter medications that are not covered and transportation for visits. These costs are usually borne by patients and their families and may or may not be relevant to an economic analysis depending on the perspective, the health care system and its reimbursement practices. In

Germany, a portion of the costs traditionally thought of as "out-of-pocket" are covered by the Sickness Funds [42], and thus form a part of the insured costs and should be addressed in German economic evaluations [43,44]. 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 [45].

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 [43]. Figure 3-1 provides the distribution by category and shows that the bulk consists of non-physician services (e.g., therapists), medications and transportation.

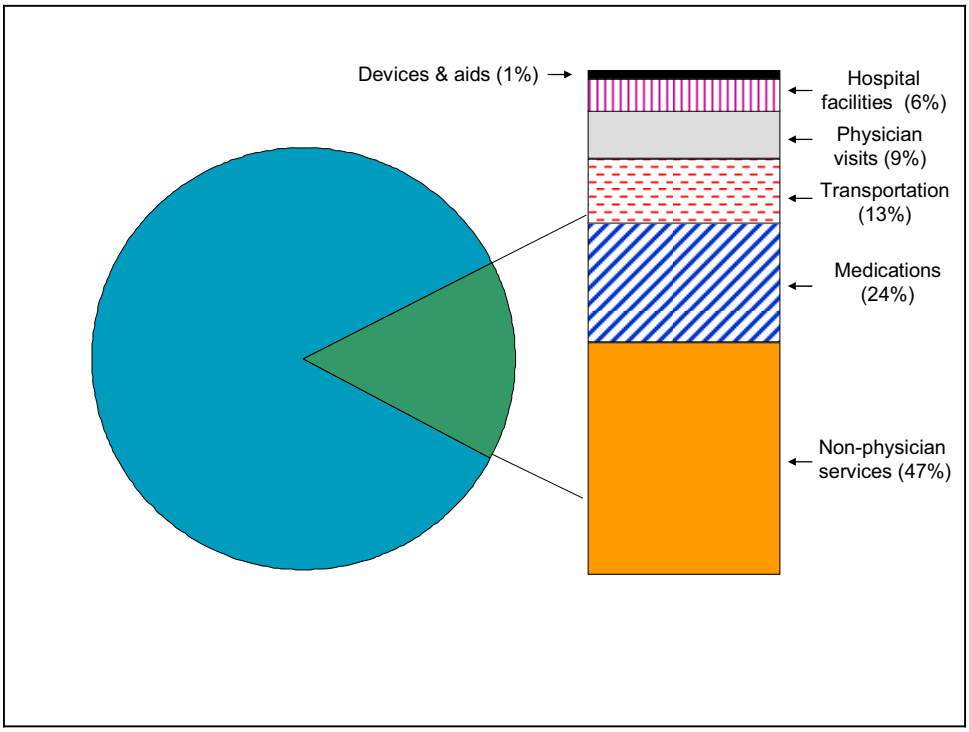

Figure 3-1 Types of out-of-pocket expenses and proportion of direct costs for management of rheumatoid arthritis in Germany (based on data from [34]).

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. If the perspective is that of the insured citizens, however, then 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 [46].

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 [47].

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, *what 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 [32]. For example, as the costs of treating patients with stroke after the acute hospitalization can be responsible for the largest proportion of expenses [24], 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 supplement.

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 [30].

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

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 [48].

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 modeled 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 assessment of uncertainty in predicted costs,**
    - **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**
- **All IQWiG models must undergo rigorous peer-review, 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 (modeling) 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 modeling 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 modeled. In effect, any evaluation that extends beyond direct application of observed data can be considered a model [49], and even direct application usually involves some form of statistical modeling. 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 supplement will describe modeling approaches in health care and provide guidance on the process of developing economic models, preferred modeling techniques, and reporting of modeling 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 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 lag time 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

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 modeled, 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 supplement.

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 [22,37,50,51], the recommended rate in Germany is at present 5% [52]. 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%, 3%, 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 modeling, 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 healthcare 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. A detailed description of modeling and BIA will be provided in the technical supplements.

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.**

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