Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Institute for Quality and Efficiency in Health Care

General Methods for the Assessment of the Relation of Benefits to Costs

Version 1.0 – 19/11/2009

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In the following text the abbreviated term *health economic evaluation* is used instead of *General Methods for the assessment of the relation of benefits to costs.*

Preamble

The Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) evaluates the benefits, harms, and economic implications of interventions to contribute to the continuous improvement in the quality and efficiency of health care in Germany. These evaluations are done to support the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) and the National Association of Statutory Health Insurance Funds (Spitzenverband der Gesetzlichen Krankenversicherung, GKV-Spitzenverband) in fulfilling their legal duties. The G-BA requests that the assessment of benefits and costs is carried out by comparing competing health technologies in a given therapeutic area. Additional costs have to be assessed in relation to additional therapeutic benefit of alternative interventions. The Institute's aim is to develop the independent scientific capacity to answer the research questions posed to evaluate medical issues and concepts relevant to health care, and to investigate research requirements relevant to patients' needs. The information compiled is relayed to the Federal Ministry of Health (Bundesministerium für Gesundheit, BMG), the G-BA, and the public. The Institute fulfils its duties by producing reports on specific topics requested by the G-BA or the BMG. It also initiates, coordinates, and publishes scientific projects to enhance health care knowledge in specific areas.

The health economic evaluation is carried out to assist the GKV-Spitzenverband in setting the appropriate maximum reimbursable price of medications on behalf of the Statutory Health Insurance (SHI) insurants. The Social Code Book V (Sozialgesetzbuch V, SGB V) requires that the assessment of benefit is conducted according to the standards of evidence-based medicine (EBM). A subsequent health economic evaluation has to be conducted in compliance with the relevant internationally recognized standards, particularly in the field of health economics. Even if international standards on individual methodological aspects, such as discounting, choice and description of the perspective for a health economic evaluation already exist, and these standards have been taken into account when preparing these methods, they are by no means uniformly and internationally applied. The methods presented here aim to be consistent with generally accepted principles of health economic evaluation while at the same time being suitable for use under the prevailing conditions in Germany.

The assessment of the relation of benefits to costs with the purpose of setting a maximum reimbursable price by the GKV-Spitzenverband is only acceptable if there is an appropriate alternative for the intervention in question, as medically necessary treatment must be available to all insured persons without restrictions. If a maximum reimbursable price is set, a potential co-payment must not lead to the abandonment of a medically necessary treatment without an adequate alternative.

Another significant restriction in the assessment of the relation of benefits to cost is that the health economic evaluation will only address those health technologies that have been judged

to be superior in comparison to existing ones (additional patient relevant benefit or less harm). This implies that the additional benefit or less harm to be considered in the health economic evaluation have been assessed by IQWiG following its published methods based on the principles of EBM. This has several implications. For example, new inferior therapies will not be economically evaluated, even if they are considerably less expensive than existing ones.

Health 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 providers, and organizational structures. Therefore, IQWiG defines project-specific methods and criteria for preparing assessments of drug and non-drug health technologies and summarizes these in the report plan. Not all steps in an evaluation process can be presented in advance and in detail in every case. Individual procedures and their results are, amongst other things, dependent on the particular research question, the evidence available, and any comments received in the hearing procedure. This document describes the principles by which the efficiency of the technology in question can be compared with the efficiency of existing technologies in a therapeutic area. The above-mentioned restrictions apply to the actual guideline's implementation.

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List of abbreviations

AG	Working Group
BMG	Federal Ministry of Health
DRG	Diagnosis Related Group
EBM	Evidence-Based Medicine
EQ-5D	European Quality of Life – 5 Dimensions
ESSEC	École Supérieure des Sciences Économiques et Commerciales
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GKV	Gesetzliche Krankenversicherung (Statutory Health Insurance)
ICES	Institute for Clinical Evaluative Sciences
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MDS	Medizinischer Dienst der Spitzenverbände der Krankenkassen e. V. (Medical Review Board of the Statutory Health Insurance Funds)
MTC	Mixed Treatment Comparison
QALY	Quality Adjusted Life Year
SGB	Sozialgesetzbuch (Social Code Book)
SHI	Statutory Health Insurance
UMIT	University for Health Sciences, Medical Informatics & Technology (Austria)

Summary

Background

This report describes a method to be used for the health economic evaluations generated by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG). The method serves as guidance to prepare topic-specific report plans regarding health economic evaluations that the contracting bodies have commissioned IQWiG to undertake. The evaluations conducted by IQWiG will address the appropriateness of prices of health technologies and provide information to the National Association of Statutory Health Insurance Funds (Spitzenverband der Gesetzlichen Krankenversicherung, GKV-Spitzenverband) for setting a maximum reimbursable price for these technologies. The evaluations are carried out after the intervention has been approved (i.e. *ex post*).

It is important to mention that IQWiG was not commissioned to develop a method enabling priority-setting within the health care system. In other words, it is not about comparing the value for money of a new intervention with that obtained in health care in general (i.e. in other therapeutic areas). The challenge was to examine how information on existing alternative interventions in a given therapeutic area may serve as guidance to decision makers in setting maximum reimbursable prices.

Method

The key features of the proposed method are:

1. After a benefit assessment by IQWiG, this benefit is transferred to the health economic evaluation.

2. There are two basic considerations concerning the evaluation of benefit for insured persons:

    a. For the relation of benefits to cost to be meaningful, the assessed benefit must be measured (approximately) on a cardinal scale.

    b. A model may be necessary when considering prognostic implications within a health economic evaluation.

3. For each intervention to be included, the disease-related total net cost (= cost minus cost-offsets) per patient (including costs borne by patients or other cost centres) are generated according to the German context using scientifically sound methods, including modelling. The requirements of cost calculation are described in Chapter 4 of this report.

4. To present the information clearly yet comprehensively, an “efficiency frontier” plot is created (see Figure 1). Each intervention is plotted on a coordinate system as follows: net cost per patient generated by the application of the intervention on the horizontal axis (x-

axis) and the health benefit (or, where applicable, harm) generated by the application of the intervention on the vertical axis (y-axis):

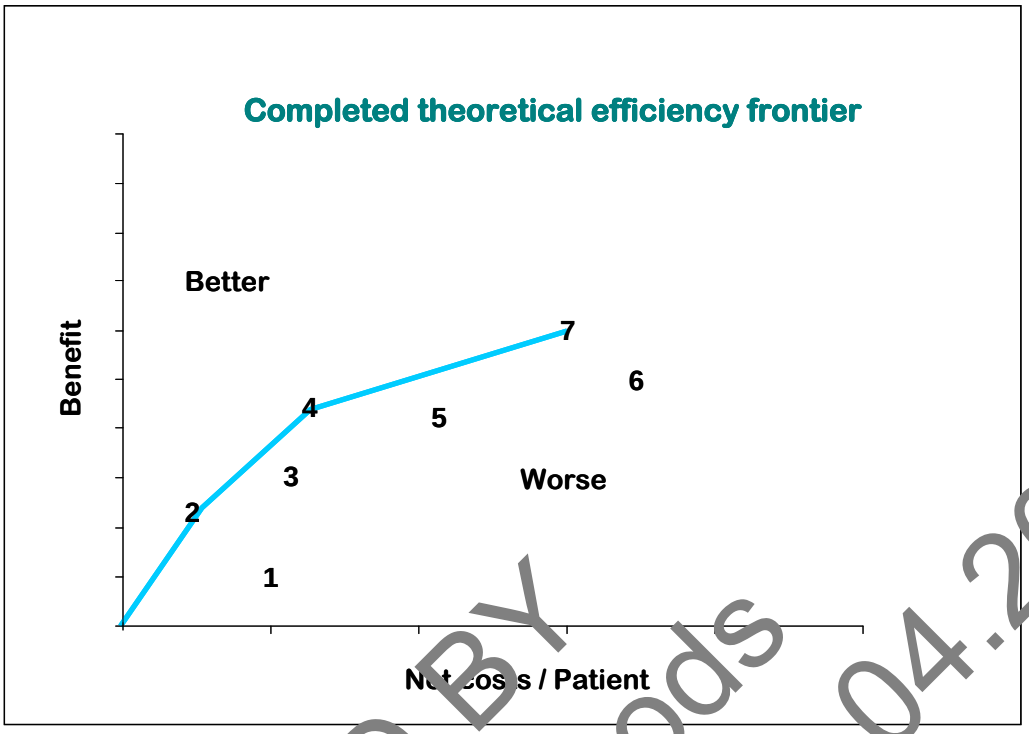

Figure 1: Completed theoretical efficiency frontier

The efficiency frontier divides the cost-benefit plane into two areas: an area with better efficiency and an area with worse efficiency. This illustration shows an ideal type of efficiency frontier and does not consider any uncertainty in the estimation.

a. The resulting figure shows decision makers how much benefit can be obtained from the resources used in the specific therapeutic area by the application of a specific intervention and allows a comparison. At a glance, the decision maker gains an impression of both the comparative cost-effectiveness ratios of and the degree of variation in treatment options. IQWiG assumes that a recommended maximum reimbursable price is appropriate for a medical intervention to be assessed, if it does not lower the efficiency of the relevant therapeutic area. The appropriate recommended maximum reimbursable price cannot be directly read off the cost axis on the graph; it is derived from the average net costs per patient that include all relevant cost components from the perspective chosen.

   i. The efficiency of any new intervention to be evaluated may be assessed relative to the plotted alternatives.

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

iii. If it is worse (i.e. below and to the right of the efficiency frontier), then it suggests that its current price is not reasonable and should be adjusted down.

iv. If it has a cost-effectiveness ratio comparable to efficient existing interventions, then its current price may be reasonable. However, this requires further evaluation (e.g. by means of a budget impact analysis), particularly for those interventions to be assessed which exceed the corresponding alternative intervention in benefit as well as in costs.

5. Some auxiliary lines indicated by the efficiency frontier may be plotted.

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

   b. Another line could indicate an average cost to benefit ratio for the cost-effectiveness ratio of existing interventions (mean cost-effectiveness ratio in the therapeutic area in question).

   c. In each case there is a theoretically based line: this line, called the theoretical efficiency frontier, connects a subset of "most efficient interventions" in the area. They are most efficient in the sense that none of them is dominated by other interventions – neither absolutely (i.e. there is no other intervention that is at once less costly and more valuable), nor in an extended fashion (i.e. there is no pair of interventions whose weighted average would yield more value at less cost).

6. Decision makers can use the efficiency frontier as a guideline by looking at the position of a new intervention in relation to the position of established interventions. If there are various efficiency frontiers, the following statements apply solely specific to each outcome. If different outcomes have been aggregated into a single unit, the following statements apply without restriction.

   a. If the new intervention is more efficient than the comparator with the highest value on the efficiency frontier, there is no necessity to set a lower maximum reimbursable price.

   b. If the new intervention is less efficient than the comparator with the highest value on the efficiency frontier, it is assumed (based on the benefit of the product) that its maximum reimbursable price is set to be consistent with the highest existing efficiency in its therapeutic area. If the main objective is to prevent a decrease in efficiency in the health care system, then the acceptance of prices that fall short of the hitherto lowest efficiency requires additional justification.

   c. The price for the intervention to be assessed is then considered appropriate if it does not lead to a deterioration of efficiency in a therapeutic area.

d. If different aspects of the benefit of the intervention cannot be combined, several efficiency frontiers have to be plotted. The two levels should be differentiated according to whether several indications are involved or whether, in addition, several aspects of benefit or harm are involved within one or several indications.

   A price can be appropriate if it does not lead to a deterioration in efficiency in at least one non-marginally weighted aspect of benefit. The separate weights of the benefit aspects can be integrated in the recommendations for a maximum reimbursable price, in compliance with the decision maker's preferences. Similar considerations can be made if a drug to be assessed is approved for several indications.

7. The effective market price of health care goods does not necessarily correspond to the SHI insurants' willingness to pay for the relevant benefit. This results from the fact that there is no complete market for the health care services of the SHI. If a certain willingness to pay for particular services were to be identified in the future, it could be included on the chart. This would form an additional criterion for the decision maker to set a maximum reimbursable price based on a recommendation.

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

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

   b. The diagram also shows inefficient interventions for specific endpoints (i.e. those that are both more costly and less beneficial than other existing options).

9. Subsequently, a budget impact analysis will be performed which will serve as an aid for the decision makers as it gives estimates of the possible consequences on health care expenditure. In this way, the reasonableness of the coverage of costs by the insurants may be judged.

Conclusion

Based on information concerning the relation of benefits to costs of existing interventions in a given therapeutic area, comparisons of the resulting efficiency can be used to derive guidance for the setting of maximum reimbursable prices.

CHAPTER 1

1 Introduction

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

1.1 General conditions

This document has been generated in accordance with a set of general conditions which stipulate the legal requirements as well as the scientific context that serve as a basis for the development of methods regarding the economic evaluation of health technologies for IQWiG. German legislation defines the legal requirements determining the approach to assessing the relation of benefits to costs of health technologies in the Social Code Book V (Sozialgesetzbuch V, SGB V).

1.1.1 Legal framework

After the "Act to promote competition among the statutory health insurance funds" (*GKV-Wettbewerbsstärkungsgesetz* [1]) came into force on 1 April 2007, the assessment of the benefits and costs of drugs was introduced as a task for IQWiG (§ 139a (3) clause 5 SGB V). This assessment primarily concerns prescription drugs that have recently entered the health care system or important prescription drugs that are already available (§ 35b (1) SGB V). To undergo health economic evaluation, health technologies have to possess an additional benefit compared to other health technologies already available or other therapeutic alternatives in use in the health care system (§ 31 (2a) SGB V). IQWiG was appointed by legislation to evaluate the relation of benefits and costs of health technologies when commissioned by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) (§ 139b (1) and (2) SGB V). Within the framework of the law, IQWiG has to ensure that the assessment of the medical benefit of health technologies is conducted according to internationally recognized standards of evidence-based medicine (EBM) (§ 35b (1) and § 139a (4) SGB V). The health economic evaluation has to be conducted according to the relevant internationally recognized standards in the field of health economics (§ 35b (1) and § 139a (4) SGB V).

1.1.2 Technology diffusion) insurants may not be deprived of access to beneficial health technologies on cost grounds alone

As a basic principle, Statutory Health Insurance (SHI) insurants may not be deprived of access to beneficial health technologies on cost grounds alone (§ 12 SGB V and § 27 SGB V).

In consequence, effective therapies are initially adopted regardless of price. Recognizing that this approach will not be permanently sustainable, the legislation now provides an instrument to define the maximum reimbursable price, fixing the limit up to which health insurance funds can reimburse costs. For this purpose, IQWiG has developed a method for the health economic evaluation of drugs and other interventions. Assessments of the relation of benefits to costs based on this method are then submitted to the G-BA as recommendations for decision making.

1.1.3 Indication-specific assessment

The indication-specific health economic evaluation is essentially based on § 12 SGB V (efficiency principle) and § 71 SGB V (stable contribution rates). According to § 71 (1) SGB V, the medical care required (once efficiency reserves have been exhausted) can enforce a derogation from the basic principles of stable contribution rates. Furthermore, according to legislation (§ 35b (1) & § 31 (2a) SGBV), the aim is thereby provided to fix a maximum reimbursable price up to which a superior health technology in a therapeutic area will continue to be funded. The Federal Ministry of Health (Bundesministerium für Gesundheit, BMG) interprets this as follows: "The effective and economic achievement of a therapeutic goal shall be paramount when prescribing a drug for any indication" (§ 12 SGB V) [2].

For the GKV-Spitzenverband, the upper limit for funding the benefit achieved represents the maximum reimbursable price. This decision is based on the evaluation carried out by IQWiG. The first step of this evaluation assesses the existence of an additional benefit in contrast to existing therapy alternatives, and only after this procedure has been commissioned will the assessment of costs and benefits take place. If an intervention shows additional benefit or a lesser harm in several aspects of benefit or therapeutic areas, the determination of several efficiency frontiers may be required. If the decision maker requires an aggregation of benefit and harm parameters in an efficiency frontier in future, IQWiG can advise on the methodology and content of prioritizing and weighting benefit and harm aspects.

An assessment of cost-benefit relations with the intention of having a maximum reimbursable price set by the GKV-Spitzenverband is only permissible when an appropriate alternative exists for the intervention that is being investigated, since all insured persons must still have full access to medically necessary interventions without restriction. The intention of the health economic evaluation is thus neither to establish priorities for resource consumption across the whole health system nor to take account of associated trade-offs.

1.1.4 Perspective

The perspective of a health economic evaluation affects the estimation of costs. Depending on the type of perspective, some costs are not regarded as expenses and thus are not considered in the cost estimation. Furthermore, there are varying degrees of difficulty, depending on the

level of aggregation of costs (micro or macro costing), when trying to separate out those cost-pools which are relevant for the particular perspective.

On the basis of German law (§ 35b (1) SGB V), as a general rule the perspective must be that of the SHI insurants. Based on this perspective, the disease-related benefits covered by SHI are reflected as well as co-payments by insurants. It is emphasized that this perspective is not that of the SHI but rather of the SHI insurants.

Many international health economic guidelines recommend a comprehensive, societal perspective for the estimation of costs. However, this perspective is rarely implemented due to practical difficulties [3]. Furthermore, it should be stated in this context that none of the clinical practice guidelines of countries which have a long tradition of health economic evaluation, e.g. Australia, England and Wales, include the societal perspective. In Australia as well as in England and Wales, the health system or National Health Service perspective alone is adopted. In England and Wales this perspective can then be extended to a perspective including other social systems or the public sector, and is decided on a case-by-case basis. However, productivity losses are never considered [4,5].[1]

The consideration of a perspective that includes several other social insurance agencies as opposed to only the SHI insurants' perspective (e.g. statutory long-term care insurance, pension insurance), as well as the societal perspective that considers cost-related productivity losses (indirect costs), depends on the commission and is related to the relevant costs of the medication under consideration. The relevant costs are described in the preliminary report plan and submitted for review. The results based on an extended perspective are made available to the decision maker separately. The decision to include other perspectives in health economic analyses depends solely on whether this is relevant for the decision maker.

1.1.5 Restrictions relating to the application of utility-based aggregation measures

Many countries use a universal threshold across all indications for health economic evaluation. There is no such threshold in Germany.

Health economic guidelines usually request that the health economic evaluation of a technology takes the question of resource allocation across the entire health care system into account [6]. Consequently a search was undertaken under the guidance of the expert committee advising IQWiG to obtain an overview of internationally common aggregated parameters for the determination of benefit, e.g. quality-adjusted life years (QALYs). However, in many countries cost-utility analyses based on QALYs are not accepted by decision makers and clinicians due to concerns regarding solidarity, equity and fairness. The

[1] Oral communication from Dr. Ruth Lopert (previously Pharmaceutical Benefits Advisory Committee, now Therapeutic Goods Administration, Australia).

trend today is to ask how such distributive concerns may be given greater weight in economic analyses [7].

The use of QALYs specific to each therapeutic area is not ruled out by IQWiG, but there are ethical and methodological concerns arising from certain survey instruments, such as time trade off and standard gamble, to consider prior to implementation. The use of aggregated efficiency measures across therapeutic areas inevitably involves judgements about the societal understanding of treating different diseases as well as about their relative benefit (even if only implicitly). No universally accepted method has yet been found. Instead, the IQWIG method takes a rather pragmatic approach aimed at comparing the efficiency of treatments in a therapeutic area, without addressing the broader issue of prioritizing across the health care system. Thus, the evaluation aims to inform the decision maker about the efficiency of a given technology compared to existing technologies in that therapeutic area, but it does not attempt to judge whether a particular condition deserves treatment relative to others or how much should be spent on it. Decision making about social priorities and values is left to the decision-making bodies designated by law.

1.2 Process of creating the guideline

The present document "General Methods for the assessment of the relation of benefits to costs, version 1.0" has three predecessors, as shown in Table 1.

Title of document	Publication date	Notes	Translation
Methodik für die Bewertung von Verhältnissen zwischen Nutzen und Kosten im System der deutschen gesetzlichen Krankenversicherung – Version 1.0	24/01/2008	**Draft** followed by hearing process	Methods for the assessment of the relation of benefit to costs in the German statutory health insurance system – version 1.0
Methodik für die Bewertung von Verhältnissen zwischen Nutzen und Kosten im System der deutschen gesetzlichen Krankenversicherung – Version 1.1	14/10/2008	**Draft** followed by comments from the Scientific Advisory Board	Methods for the assessment of the relation of benefit to costs in the German statutory health insurance system – version 1.1
Entwurf einer Methodik für die Bewertung von Verhältnissen zwischen Nutzen und Kosten im System der deutschen gesetzlichen Krankenversicherung – Version 2.0	13/03/2009	**Draft** followed by hearing process	No translation available
Allgemeine Methoden zur Bewertung von Verhältnissen zwischen Nutzen und Kosten – Version 1.0	19/10/2009	**Final** paper	General Methods for the assessment of the relation of benefit and costs – version 1.0 (version date: 19/11/2009)

Table 1: Chronological overview of the different versions of IQWiG's methods paper for the assessment of the relation of benefit to costs and their respective translations

The development of the current document and its predecessors was the result of a consultation process between international experts. Chairman of this panel was Prof. Jaime Caro. The other experts on the panel critically examined all versions of the methods paper and wrote numerous statements which showed partly diverging opinions regarding methodological details. In order to provide a clear insight into the framework conditions in Germany, and to

meet the requirements of IQWiG, the method developing process was accompanied by an intensive exchange with IQWiG.

The panel comprised eight international experts in the area of health economics and at the same time represented countries with long experience of health economic evaluation (e.g. Australia, United Kingdom, Canada).

Members of the IQWiG International Expert Panel

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

In addition, the Scientific Advisory Board submitted recommendations that have been included in the draft version 2.0 of the method for assessing the relation of benefits to costs in the German statutory health insurance system.

Members of the IQWiG Scientific Advisory Board

Prof. Dr. Guido Adler	Universitätsklinikum Ulm, Germany
Prof. Dr. Dr. Afschin Gandjour	Louisiana State University, Baton Rouge, USA
Prof. Dr. mult. Dominik Groß	Universitätsklinikum Aachen, Germany
Prof. Dr. Hans-Werner Hense	Universität Münster, Germany
Prof. Dr. Peter Jüni	Institut für Sozial- und Präventivmedizin, Bern, Switzerland
Prof. Dr. Johannes Köbberling	Kliniken St. Antonius, Wuppertal, Germany
Prof. Dr. Georg Marckmann	Universität Tübingen, Germany
Prof. Dr. Ingrid Mühlhauser	Universität Hamburg, Germany
Prof. Dr. Heinz Rothgang	Universität Bremen, Germany
Prof. Dr. Holger Schünemann	McMaster University, Hamilton, Canada
Prof. Dr. Jürgen Windeler	MDS, Essen, Germany

The members of the IQWiG Scientific Advisory Board convened an ad hoc working group on health economic evaluation which comprised members of the International Expert Panel as well as representatives from the field of health economics in Germany.

Members of the health economic evaluation working group of the IQWiG Scientific Advisory Board

Prof. Dr. Jaime Caro	McGill University, Canada
Prof. Dr. Dr. Afschin Gandjour	Louisiana State University, Baton Rouge, USA
Prof. Dr. mult. Dominic Gross	Universitätsklinikum Aachen, Germany
PD Dr. Christian Krauth	Medizinische Hochschule Hannover, Germany
Prof. Dr. Georg Marckmann	Universität Tübingen, Germany
Prof. Dr. Heinz Rothgang	Universität Bremen, Germany
Prof. Dr. J.-Matthias Graf von der Schulenburg	Universität Hannover, Germany
Prof. Dr. Uwe Siebert	UMIT, Hall in Tirol, Austria
Prof. Dr. Jürgen Windeler (moderator)	MDS Essen, Germany

Over the course of three workshops, a draft recommendation was prepared by the working group for the Scientific Advisory Board. On the basis of this draft, the Scientific Advisory Board recommended that IQWiG revise the methods paper. On the basis of this recommendation, IQWiG produced the current version 1.0. Working papers to replace the technical documents will be published as supplements to version 1.0.

1.3 Structure of the methods paper

The proposed methods for assessing the relation of benefits to costs in the German statutory health insurance system are described in this document, dealing with the development of topic-specific procedures (report plans).

Following an introduction, the main document is divided into six sections:

- Producing a report on a health economic evaluation
- Benefit assessment
- Cost estimation
- Modelling
- Efficiency frontier concept
- Recommended actions

CHAPTER 2

2 Producing a report on a health economic evaluation

The assessment of the relation of benefits to costs is one of several scientific assessments carried out by IQWiG. All scientific assessments, including the health economic evaluation, are part of established procedures, which are described in General Methods of IQWiG [8] in Chapter 2 “The Institute’s products”.

If health economic evaluation is to be used to set a maximum reimbursable price, the legal framework laid down in § 35b SGB V applies. The Social Code Book (SGB) also states that certain groups of individuals have to be involved to an appropriate extent. IQWiG meets this requirement by giving the opportunity to submit written comments at each step in the process. This process is shown in Figure 2. All working steps taken are under the Institute’s responsibility and involve external expertise where appropriate. If necessary, the Institute’s Scientific Advisory Board is also involved. The internal quality assurance process is not outlined in this flow chart.

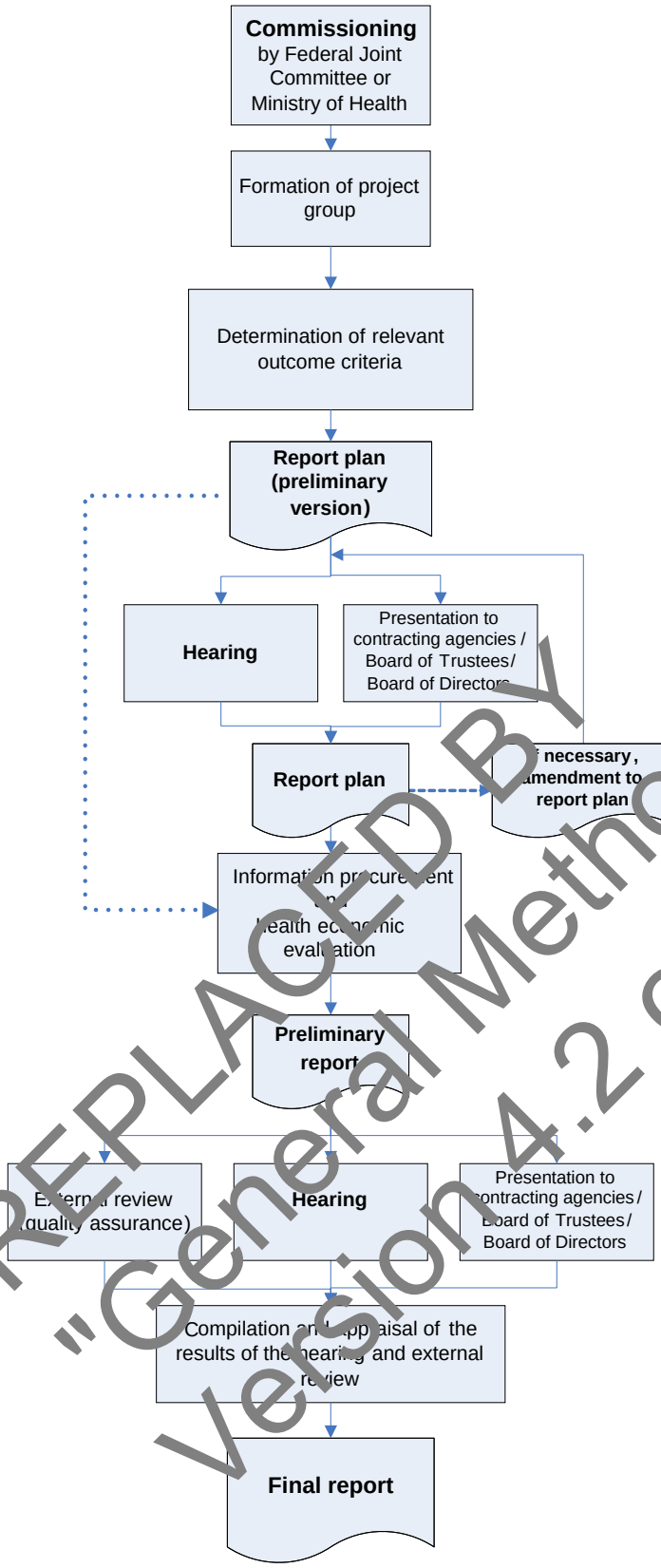

Figure 2: Process

After commissioning by the G-BA or BMG, the Institute's internal project group is formed under the supervision of the department concerned. The research question is worded in consultation with the contracting body's responsible committees, involving external professional expertise or consulting individuals concerned, if appropriate. The report plan is subsequently prepared.

The report plan, comparable to the study protocol of a clinical trial, contains the precise scientific research question, including a description of the project-specific methodology applied in the information procurement and in the assessment of the information retrieved. The transfer of the additional benefit or lesser harm obtained in the preceding benefit assessment into the health economic evaluation is described in the report plan. This plan is prepared under the responsibility of the IQWiG project group, usually involving external experts. After completion of the internal quality assurance process and approval by the Institute's Steering Committee, the preliminary version of the report plan is then forwarded to the contracting body (also to examine its completeness in respect of the commission originally awarded). It is also forwarded to the Board of Trustees and the Foundation's Board of Directors. The preliminary version of the report plan is then published on the Institute's website (usually 5 working days later) in order to provide the opportunity to submit comments.

The hearing procedure (written comments and optional oral debate) is explained on the IQWiG website in a guideline that applies equally to all procedures (http://www.iqwig.de/submission-of-comments.507.en.html). For a period of at least 4 weeks, the public is given the opportunity to submit written comments (hearing procedure). This includes medical, pharmaceutical, and health economic experts from research and practice, professional representatives of pharmacists, pharmaceutical manufacturers, manufacturers of medical devices, the relevant organizations responsible for representing the interests of patients and self-help groups of chronically ill and disabled persons, as well as the Federal Government Commissioner for Patients' Affairs. This enables an open and independent reviewing procedure for the report plan. The opportunity to submit comments refers especially to the project-specific methodological approach. At the same time, the opportunity is also provided to submit any type of document of appropriate quality (especially unpublished data) which is suited to answer the research question of the report, in the opinion of the person submitting comments. An adequate justification of the suitability of the documents is necessary. Should any objections relating to the commission be raised during this procedure (e.g. comparative therapy), they are forwarded to the G-BA for scrutiny. IQWiG's hearing procedure also has the option of holding an oral scientific debate with those submitting comments. This debate may help clarify any aspects of the written comments and improve the scientific quality of the report plan. In order to avoid undue delay of the Institute's work, the comments must fulfil certain formal requirements.

Further information on the commenting procedure of the preliminary report plan and the resulting amendments to the report plan is published on the IQWiG website in the relevant

guideline (http://www.iqwig.de/submission-of-comments.507.en.html). The conditions stated in the current version of this guideline apply.

After the analysis of the comments, the revised report plan is published together with the results of the hearing (i.e. written comments submitted; meeting minutes of the [optional] oral scientific debate; appraisal of comments). This report plan is the basis for the preparation of the preliminary report. If further relevant methodological changes are required in the course of the preparation of the preliminary report, these are usually presented in one or several amendments to the report plan. An opportunity to submit comments is usually also provided after publication of an amendment, following the conditions outlined above.

The results of the information procurement and the scientific assessment are presented in the preliminary report. In order to avoid undue delay in the Institute's work, the information procurement and assessment start before completion of the commenting procedure on the report plan on the basis of the criteria formulated in the preliminary report plan. However, the results of the commenting procedure is explicitly not anticipated, as these criteria may be modified on the grounds of the comments on the preliminary report plan, which may lead to supplementing and/or modifying the information procurement and assessment.

The preliminary report includes the preliminary recommendation to the G-BA. It is produced under the responsibility of the IQWiG project group, usually with the involvement of external experts. After completion of the internal quality assurance process and approval by the Institute's Steering Committee, the preliminary report is then forwarded to the contracting body (also to examine its completeness in respect of the commission that was originally awarded). It is also forwarded to the Board of Trustees and the Foundation's Board of Directors. An additional step in the quality assurance of the preliminary report is a review conducted by one or several external experts with recognized methodological and/or topic-related competence. The preliminary report is published on the Institute's website (usually 5 working days after delivery to the contracting body) in order to provide the public with the opportunity to submit written comments (hearing procedure) for a period of at least 4 weeks. This includes medical, pharmaceutical and health economic experts from research and practice, professional representatives of pharmacists, drug manufacturers, manufacturers of medical devices, relevant organizations responsible for representing the interests of patients and self-help groups of chronically ill and disabled persons, as well as the Federal Government Commissioner for Patients' Affairs. This enables an open and independent reviewing procedure for the preliminary report. The topics addressed in the commenting procedure refer in particular to the results of the information procurement and assessment presented in the preliminary report. At the same time, the opportunity is also provided to submit any type of document of appropriate quality which is suited to answer the research question of the report in the opinion of the persons submitting comments. An adequate justification of the suitability of the documents is necessary.

Optionally, an oral scientific debate may be held attended by those submitting comments. This debate serves to clarify, if necessary, any aspects of the written comments, and aims to improve the scientific quality of the final report. In order to avoid undue delay in the Institute's work, the comments must fulfil certain formal requirements. Further information on the commenting procedure for the preliminary report is published on the IQWiG website in the relevant guideline (http://www.iqwig.de/submission-of-comments.507.en.html). The conditions stated in the current version of this guideline apply.

The final report, which is based upon the preliminary report and contains the assessment of the scientific findings (taking the results of the hearing into consideration) represents the final product of the work on the commission. It is produced under the responsibility of the IQWiG project group, usually involving external experts. After completion of the internal quality assurance process and approval by the Institute's Steering Committee, the final report is initially forwarded to the contracting body and subsequently (usually 4 weeks later) forwarded to the Board of Trustees and the Foundation's Board of Directors (together with the documentation of the written comments, the meeting minutes of the [optional] scientific debate, and the appraisal of the comments). These documents (final report and documentation/appraisal of comments) are then published on the IQWiG website (usually a further 4 weeks later). If comments are received on final reports that contain substantial evidence not considered, or if the Institute receives information on such evidence from other sources, the contracting body will be sent well-founded information as to whether or not, in the Institute's opinion, a new commission on the topic is necessary (report update). The contracting body then decides on the renewed commissioning of the Institute. The general methodological and procedural requirements for the Institute's products apply in the updating process.

CHAPTER 3

3 Benefit assessment

The methods used to determine benefit in a benefit assessment are described in IQWiG's General Methods [8]. The most important aspects of a benefit assessment for the health economic evaluation are only briefly described here.

3.1 Result of benefit assessment

For the purposes of benefit assessment, "benefit" is described as a causally determined positive effect and "harm" as a causally determined negative effect of medical interventions with regard to patient-relevant outcomes. The definition of "benefit" and "harm" is therefore based on the evaluated intervention.

Benefit and harm are determined by comparison with placebo (or other sham treatments) or no treatment. When comparing the medical measure to be evaluated with another clearly defined medical intervention, the following terms are used for the comparative assessment of benefit and harm aspects:

- Benefit aspects:
    - In the event of greater benefit the term "additional benefit" is used.
    - In the event of lesser or comparable benefit, the terms "lesser benefit" and "comparable benefit" are used.
- Harm aspects:
    - The terms "greater", "comparable" and "lesser harm" are used; the term "additional harm" should be avoided.

If possible, benefits and harms are weighed up.

As a result of the benefit assessment, the Institute reaches one of five conclusions for each predefined patient-relevant outcome:

1. Proof of (additional) benefit or harm exists.
2. Indications of (additional) benefit or harm exist.
3. Proof of the lack of (additional) benefit or harm exists.
4. Indications of the lack of (additional) benefit or harm exist.

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

Conclusions 1) and 3) require sufficient certain evidence of an effect or lack thereof; 2) and 4) imply that there is some suggestion of an effect or lack thereof, but the evidence for proof is insufficient. In the absence of any suggestion because of insufficient data or insufficiently robust data, IQWiG selects conclusion 5).

Health economic evaluations are only performed for therapeutic areas to be evaluated for which additional benefit or lesser harm is determined for at least one outcome.

3.2 Transferring benefit into the health economic evaluation

Based on the results found during the benefit assessment, the decision is made whether to carry out a health economic evaluation. The results from the benefit assessment are integrated into the health economic evaluation and may be supplemented (see 3.2.3 "Input for determining the benefit axis in the health economic evaluation") in order to create the efficiency frontier for the treatment options. Figure 3 illustrates the transition from benefit assessment to health economic evaluation.

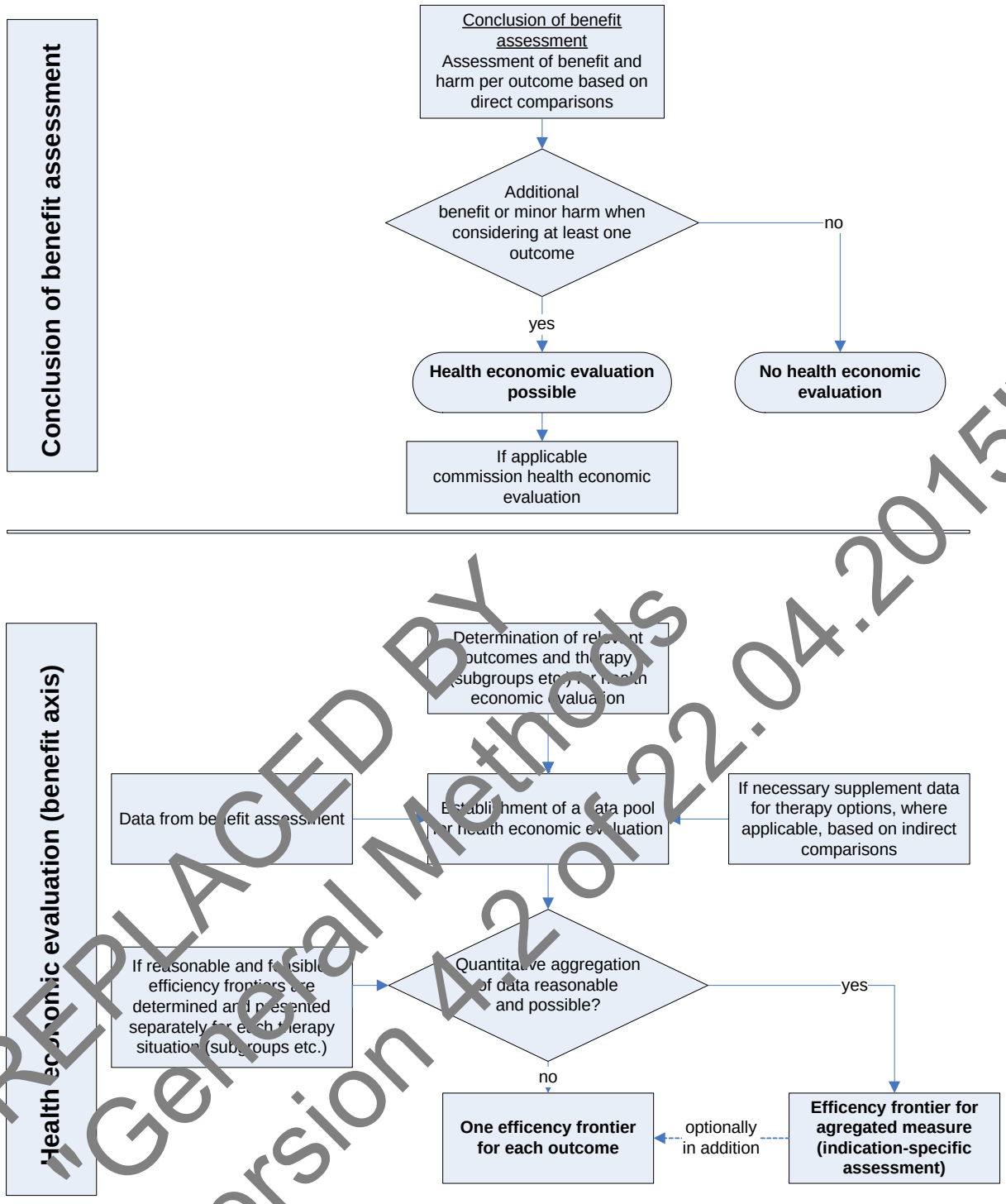

Figure 3: Benefit assessment and health economic evaluation

3.2.1 Selection of comparators

In addition to the health technology to be assessed, all therapeutic alternatives relevant in a particular therapeutic area should be included in a health economic evaluation. Comparators that are relevant in a benefit assessment are usually the same as those to be used in a health economic evaluation. If, in contrast to the previous benefit assessment, the health economic evaluation produces benefit results on additional comparators in the relevant therapeutic area by means of adjusted indirect comparisons, these results can be included in the health economic evaluation depending on how robust they are. The preliminary report plan explains this for each therapeutic area.

3.2.2 Relevant outcomes and therapy situations

A health economic evaluation can be performed if an additional benefit or lesser harm of one technology (when compared to one or more suitable treatment alternative(s)) were identified in the benefit assessment. As a rule, only those outcomes and therapy situations (e.g. patient-subgroups, indications) are assessed in the health economic evaluation for which an additional benefit or lesser harm was established in the benefit assessment.

3.2.3 Input for determining the benefit axis in the health economic evaluation

In order to assess the benefit of interventions, the Institute primarily uses direct comparisons (head-to-head comparisons). As a general rule, the information generated is based on the pair-wise comparison of treatment alternatives for which direct evidence is available. Additional benefit or lesser harm are, as a rule, only established on the basis of results derived from studies of direct comparison.

Health economic evaluations of interventions generally require common quantitative comparisons of multiple (more than two) interventions. In this instance, limiting it to direct head-to-head comparisons would imply that the health economic evaluation is limited to a single comparison by pairs or is even not feasible at all. In order to allow for health economic evaluations of multiple interventions, the Institute can also use indirect comparisons to assess the relation of benefits to costs, thus accepting a lower reliability of results compared to the pure benefit assessment approach. However, appropriate methods for the estimation of results derived from indirect comparisons have to be employed. The Institute rejects the use of non-adjusted indirect comparisons (i.e. the naïve usage of individual study arms) [9-11]. Generally, a mixed treatment comparison" (MTC) meta-analysis [12,13], which is also called "multiple treatment meta-analysis" [14] or "network meta-analysis" [15,16] is considered an appropriate approach. Apart from the assumption of paired meta-analyses (e.g. no significant heterogeneity), there also needs to be sufficient consistency in the effects estimated in individual studies. The latter is a critical issue, since MTC meta-analyses only provide valid results when consistency is guaranteed. Although techniques for investigating inconsistencies are currently being developed [12,17], this topic still has many unanswered methodological

questions [18,19]. Thus, the aim is to fully describe the model used and clarify any unsolved issues in the report plan [19].

To carry out a health economic evaluation, the data used for the benefit assessment can be extended by studies which may add indirect comparisons to the benefit axis of the efficiency frontier. However, indirect comparisons may not generate any (additional) benefit that could not be shown in direct comparisons or placebo-controlled trials.

3.2.4 The term “benefit”

In health economic literature, the term “benefit” is used both in a narrow and in a wider sense. In its narrow sense it is based on EBM and reflects the pure medical benefit in evaluating a measure. In its wider sense, the term "benefit" includes not only the effects of an intervention, but also what is described in health economics literature as “value”. An example is the preference-based “valuation” of benefit. To represent the relation of benefits to costs, IQWiG can plot on the benefit axis an approximately cardinally scaled benefit (derived directly from study results where necessary), or a transformed approximately cardinally scaled benefit. The term “benefit” will be used below in its narrow or wide sense depending on the context.

For the integration of the benefit into the health economic analysis by means of the efficiency frontier, the benefit needs to be (approximately) cardinally scaled. This requirement means that, for instance, two increases considered to be equal in size actually correspond to an identical growth in benefit.

Limiting the condition that a benefit "only" has to be approximately cardinally scaled is based on the following considerations:

1) A scale used to measure benefit does not have to be entirely cardinally scaled across its entire range. It is sufficient if it is cardinally scaled across the range relevant to the definition of patient-relevant additional benefit. Different survey instruments will often show bottom or ceiling effects at the margins of their ranges, yet are cardinally scaled across the remaining range [20-22].

2) A benefit on a ratio scale can also be assumed to be approximately cardinally scaled over a range relevant to the benefit assessment.

The patient-relevant benefit of diagnostic and therapeutic interventions is identified in controlled clinical trials. Many commonly-used measures of benefit are not cardinally scaled and thus are not appropriate instruments to measure the benefit of a change in health status. In health economics, there are various instruments that purport to cardinally measure how people value certain changes in their health. These instruments encompass question techniques like the standard gamble, the time trade-off and the person trade-off [23], or the application of multi-attribute utility instruments [24], such as the Health Utilities Index [25,26] or health status scoring systems such as the EQ-5D [27,28]. Furthermore, the procedures can deliver

summary measures when the effects of interventions are multidimensional (for instance, have several positive functional effects as well as some side effects).

In the present methodology, no specific instrument or procedure to cardinally measure benefit is recommended. Each therapeutic area may offer different possibilities to measure benefit in a way to ensure that the cardinality requirement is met. Potential users of the proposed methods are urged to bear in mind the distinction between the effect and the requirement that the effect be approximately cardinally scaled.

For those time periods where there are no studies on the efficiency of medical interventions, study data could be used to simulate the benefit by means of mathematical modelling techniques. The models employed are designed to provide prognoses regarding events occurring during the course of a disease. Yet, models should not generate new patient-relevant (additional) benefit which is not based on the results of studies, and which might lead to a reversal in the superiority of the technologies under consideration. The benefit must be established on the basis of study data from the previously performed benefit assessment.

3.2.5 Representation of benefit on the benefit axis

Health economic evaluations in Germany are not to serve as a basis for general allocation decisions across all therapeutic areas. Thus, there is no need for a universal measure of benefit determination, that is, for a measure that covers all potential aspects. It is important for all participants that instruments used to measure benefit in a therapeutic area are defined well in advance of an evaluation.

The benefit can be represented on the benefit axis of the efficiency frontier graph by employing clinical measures, responder measures or aggregated measures. If several benefit measures are shown next to each other, an efficiency frontier will be plotted for each relevant benefit measure.

Clinical measures

The primary clinical measures used by IQWiG are mortality, morbidity, health-related quality of life and validated surrogates. Surrogates have to meet the criteria stipulated in the IQWiG's General Methods 3.0 [8].

If health economic evaluations are carried out using different clinical measures, an efficiency frontier needs to be established for each one of these measures.

Responder measures

Another approach for parameterizing the benefit is to estimate the likelihood that a patient will respond (i.e. achieve a specified therapeutic goal). To do this, the responder concept has to be defined for each therapeutic area [29]. Responder definitions already exist for many illnesses and are even used as primary outcomes in clinical trials [30,31]. If no responder concept has been defined (until now), or none is consistently used as the basis for evidence in

a particular therapeutic area, an important step in the evaluation could be to develop this definition autonomously, providing the requirements are in place [32].

Aggregated measures

Another way of representing the benefit on the benefit axis of the efficiency frontier graph is to aggregate different benefits into one single measure and then to establish one single efficiency frontier.

Since health economic evaluation in Germany should not be performed across indications, but only within individual therapeutic areas, single indication-specific aggregated measures can be employed. It is not necessary to use primarily aggregated measures which can be applied across indications. The use of such measures, e.g. the QALY, can however be reasonable for the comparison of interventions within a therapeutic area, if there is no other validated instrument for aggregating the assessment of benefit and harm in this area. The indication-specific use of QALYs can be particularly useful with new drugs whose life-extending effect is considerably offset by the reduction of quality of life caused by side effects.

In this case, the ethical and methodological problems surrounding the equity of QALYs would not apply. However, if the QALYs are not recorded in the target group, the methodological problem remains of whether they may be transferred from other contexts or from surveys of the general population to the specific context in question.

3.2.6 Outcome weighting

The prioritization and weighting of outcomes is important if the assessed benefit is multi-dimensional. Multi-dimensional benefit is operationalized by the presence of several patient-relevant outcomes. The analysis of the efficiency frontier can be simplified by weighting the individual patient-relevant outcomes. An assessment is done for a selection of those outcomes that were weighted higher relative to the remaining outcomes. Alternatively, the analysis can be carried out for all outcomes for which a patient-relevant additional benefit has been obtained. The results of both the weighted and the disaggregated analysis are to be presented to the decision maker. This also provides the decision maker with the option of setting a calculated mixed maximum reimbursable price. In addition, weighting individual patient-relevant outcomes represents a premise for benefit aggregation, as it cannot be assumed per se that outcomes are incorporated in an aggregated measure with equal weights.

Methods on prioritizing and weighting outcomes are detailed in the preliminary report plan, if required by the commission. Analytic hierarchy process and conjoint analysis are just two of the methods for weighting outcomes that are investigated by IQWiG in collaboration with international experts.

CHAPTER 4

4 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 assessment of benefit and harm, there is no general "cost" that will hold across time, place and other aspects [33]. To be useful to the decision maker as well as to form the basic input for a health economic model, these evaluated costs must be reported in sufficient detail and must be appropriately adapted to the particular context. The approaches for the estimation of costs illustrated in the following sections are consistent with internationally approved principles of health economic evaluation.

4.1 Direct costs

Approach:

Health economic evaluations carried out on behalf of IQWiG have to consider direct costs.

Direct medical costs reflect the monetary value of resources that are consumed through the provision of a specific health service and which are reimbursed by the SHI or partly covered by additional payments from the insurants ("out of pocket expenses") [34-36]. Typical examples of these costs are a visit to the general practitioner, a hospital stay or a laboratory test. These costs form the basis for health economic analyses. Direct non-medical costs, e.g. transport costs, home help, etc. should be included in pertinent cases.

4.2 Indirect costs

Approach:

Indirect costs are not primarily considered. If loss of productivity is substantially affected by a new health technology, the corresponding costs may be evaluated separately. It should be noted that the costs are not to be listed on both the cost and benefit side. Loss of productivity due to mortality is included in the outcome on the benefit side. Loss of productivity due to incapacity for work is to be considered on the cost side as indirect costs.

4.3 Steps of cost estimation

Approach:

Four basic steps are required to estimate the costs of a condition:

- identification of resource consumption

- measuring resource consumption
- valuation of resource units
- calculating total costs of intervention options

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 information from a variety of sources. Determining which sources to use is always a balancing act between relevance, credibility, and availability.

4.3.1 Identification of resource consumption

Approach:

Identifying the resources that are to be included in the cost estimation requires specifying the perspective, selecting a timeframe for the analysis and determining the relevant health care providers. Expert opinion may be valuable in these tasks.

At the identification stage, the types of health care services that are used for managing the condition need to be determined. In other words, the question: "*Which health care services (resources) are used by patients with this clinical problem?*" must be answered. Initially, when defining resource use, this can be complemented by obtaining the opinion of clinical experts, who determine the type of resources typically consumed in treating a given condition.

This information must be supplemented by up-to-date data obtained from all available sources: hospital discharge data, cost unit databases, government and other agency reports, clinical practice guidelines, and peer-reviewed medical literature. It is advisable to develop a decision tree with therapeutic paths (including diagnostic measures if necessary) which contains all relevant subsequent events. In this way, a comprehensive identification of resource consumption is guaranteed [37].

4.3.1.1 Cost-offsets

Approach:

If cost-offsets are taken into consideration, they should be investigated in comprehensive sensitivity analyses.

The costs of new health technologies often exceed the costs of existing technologies. Such increased costs can be compensated by savings in other areas of the health system (cost-offsets).

4.3.1.2 Costs in life years gained

Approach:

If extension of life is germane to the assessment of benefits and costs, the costs of treating the illness in question during the years of life gained (future costs) should be considered in the base case study. Health care costs not associated with the target disease, known as non-intervention associated costs, are not considered in the base case study, but should be considered in separate sensitivity analyses.

4.3.1.3 Start-up costs

Approach:

In order to implement a new health technology, it may be required to fund one off investments. These start-up costs should also be identified and quantified.

They should be reported separately, by category, in the budget impact analysis (see Section 7.3) with a full explanation of the methodology and sources used for the estimation of costs.

4.3.2 Measuring the quantity of resource consumption

Approach:

Measuring the quantity of relevant resource consumption must be based on up-to-date and high quality data.

When measuring resource consumption, the frequency of use, the proportion of the relevant patient population that uses each service and the duration of that service have to be taken into account. Identifying the frequency of service use is often easier than finding the proportion of persons using the service. However, it is essential to apply the cost to as accurate a rate of users as possible. Costs for services that are very infrequently used, and are thus likely to have little impact on the results, should be described but not necessarily calculated [38].

4.3.3 Evaluation of resources

Approach:

Either a micro-costing or a macro-costing approach can be used to measure resource consumption 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 and allocate the costs to each resource identified in the profile (valuation phase). The estimation of resource consumption can be top-down (macro-costing approach) or bottom-up (micro-costing approach) [39].

The approach most frequently employed is to accept data at whatever level of aggregation is accessible in order to measure resource consumption. A very simple calculation method is the

use of administered prices, e.g. the average cost of a hospital stay based on the published costs by diagnostic-related groups (DRGs) [40].

When the perspective of society is taken into consideration, the administered prices might require adjustment to derive the opportunity costs for society. The human capital approach is mainly used in calculating productivity losses but alternatively the friction cost approach can also be used. In this case, the results must be checked using sensitivity analyses while applying the human capital approach.

4.3.4 Cost factors

Approach:

All cost data adjustments must be reported along with the original data. These also include inflation from previous years, modifications to reflect the relevant perspective, and discounting.

For many interventions, health care services need to be provided at different points in time. Consequently the costs of these services have to be adjusted for inflation. The year used to report the monetary valuation of costs must be specified. An explicit reason should be provided if the current year is not used for the monetary valuation.

As there is often a time lag between the measure of cost data and when they are used in an analysis, it is not uncommon for cost values to be inflated. Prices based on inflation assumptions should not be used as a substitute for obtaining available current data. If used, the relevant rate for the medical service in question should be employed. Should this not be possible, the general price inflation rate, as stipulated annually by the Federal Statistical Office *(Statistisches Bundesamt)*, can be employed.

Specifications regarding the selection of perspectives and the type of discounting are contained in Section 6.2.5 Time horizon or Section 6.2.6 Discounting.

4.4 Reporting of cost estimation

Approach:

Any extension of the perspective of the analysis must be stated clearly and defended. The time horizon 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 reliable sources should be employed in all cost calculations. The source must be specified by citation, described fully and a statement as to why this is the best available source should be provided. In addition, it must be publicly accessible or the information must be provided together with IQWiG's report.

A detailed description of the resource consumption profiles, as well as of the methodology used for cost estimation must be provided. Irrespective of which 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.

Resource consumption and cost information relevant to the German context should be standard for all health economic analyses. If regional implementation is required, potential variation in results by region should be specified and discussed. If German data are not used, a detailed explanation must be included and reasons for the lack of German-specific data must be provided.

Overall, the costs of an intervention should reflect the net expenditure per patient including all relevant costs from the perspective of the insured individual. All cost savings arising from the intervention should be taken into account.

CHAPTER 5

5 Modelling

The aim of health economic modelling is to generate expected values for the clinical and economic effects of therapeutic alternatives. Health economic modelling hereby provides information needed to assess the comparative efficiency of an intervention in order to define a maximum reimbursable price [41]. Modelling is frequently applied since, apart from anything else, data is available for different time periods. Furthermore, the requests by contracting bodies may necessitate the evaluation of longer time horizons. If required, IQWiG primarily carries out modelling for the time period for which evidence on benefit and harm from clinical studies exist. In a second step, health technologies can be modelled over longer periods of time.

The effects found in IQWiG's benefit assessments are entered on the benefit side into the health economic evaluation. However, economic data are usually not collected in clinical trials. If this is indeed the case, these data are often insufficient for the comprehensive costing of a health technology. Clinical trials seldom provide information on the long-term consequences of a technology. In addition, they do not always adequately and comprehensively reflect all cost aspects relevant to the German health care setting [42,43]. Moreover, protocol-induced resource consumption in clinical trials may bias cost estimation. Thus, modelling the effects of a health technology is an essential component of health economic evaluations.

The most important steps in the development of a health economic model are described briefly below and the various modelling techniques introduced. The working paper "Modelling" contains a detailed description of the approach to model development, a comprehensive description and analysis of the various modelling techniques, guidance in handling uncertainty and variability as well as the approach to model validation and model documentation.

5.1 Model development

5.1.1 Approach to model development

The following steps are recommended for developing a health economic model:

- Concise definition of the research question(s)
- Draft of an impact diagram
- Compilation of a model concept
- Systematic research for available data, if necessary, primary collection of data
- Definition of functional relations within the model
- Selection of the modelling technique (model type) for model structuring
- Implementation and programming of the model
- Model validation
- Performing the analysis (base case study and sensitivity analyses)
- Preparing the report including a transparent description of the model as well as a critical discussion with regard to model assumptions and limitations

The model needs to be of sufficient detail for the research question posed. This requires the consideration of all aspects relevant to the disease and its treatment, the inclusion of benefit and harm due to interventions, the consideration of heterogeneity, the presentation of outcomes in chronological sequence and the inclusion of data specific to the German health care system. Furthermore, the model type and the technique chosen for the analysis need to be specified.

The models need to be validated accurately. This entails considering plausibility (face validity), technical validity (verification) and external validity. Moreover, they may be compared with other relevant models (cross validation).

5.1.2 Quality criteria for the development of a model

In order to guarantee the validity and formal/content traceability of modelling studies carried out by IQWiG, the following requirements need to be met:

- Full transparency, with clearly defined and justified model inputs and assumptions

- Sufficient depth to adequately represent the disease being modelled as well as the associated costs and the relevant treatment scenarios
- Sufficient flexibility to assess multiple scenarios under varying sets of assumptions and settings
- Possibility of depicting uncertainty in the predicted costs and benefit components
- Use of data that are relevant to the German context, including not only costs but also clinical practice patterns, demographics and epidemiology

5.2 Modelling techniques

There are a number of modelling techniques that have been applied in health economic evaluations such as decision trees, Markov state-transition models with cohort or individual simulation, discrete event simulation, agent-based simulation models, transmission models, and others [44-50].

The specific modelling technique should not be determined in advance. For this reason, IQWiG has no *a priori* preference for a specific modelling technique. The choice of the appropriate modelling technique depends on the research questions embodied in IQWiG's commission from the G-BA, the characteristics of the technologies to be assessed, the disease and the general conditions.

5.3 Dealing with uncertainty

There are two major kinds of uncertainty in health economic models [51]: uncertainty caused by the variability in certain parameters (e.g. patient characteristics, cost components) and uncertainty caused by variability in model assumptions.

Variability of parameters can be due to differing characteristics of persons or patients, such as age, gender, stage of the disease, pathology, risk factor profile, etc., or arises in cost calculations. The values of these variables are either known with certainty (e.g. age, gender) or there is uncertainty surrounding their value (e.g. daily costs of hospital stay, effect estimates from clinical trials). The first is usually described as heterogeneity rather than variability. Statistical uncertainty results from the fact that model parameters are usually calculated from random samples. This uncertainty can be quantified or described, for example, as confidence interval or statistical distribution respectively.

Uncertainty due to variability in model assumptions is the result of models not fully capturing and reflecting reality due to its complexity. Therefore, models have to be based on simplifying assumptions in order to be calculable, traceable and transparent. Various methods exist to adequately handle both types of uncertainty described above.

5.4 Handling uncertainty: sensitivity analyses

The impact of uncertainty on model results has to be investigated by means of sensitivity analyses. The three main types of sensitivity analysis in use in health economic evaluations are univariate and multivariate deterministic, and multivariate probabilistic (Monte Carlo).

It is not recommended to replace univariate sensitivity analyses with multivariate probabilistic sensitivity analyses. Instead, the latter should be carried out in addition to univariate analyses, if needed, so that the influence of individual important model parameters and assumptions remains visible. Finally, structural sensitivity analyses should be carried out to analyse the impact of a change in structural model assumptions.

Sensitivity analyses can be used for several outcomes:

- For a specific intervention: on average costs and/or average benefit
- For comparing interventions: on the incremental costs and/or incremental benefit
- For comparing interventions: on the incremental cost-effectiveness ratio of the efficiency frontier

In deterministic sensitivity analyses, for example, the last gradient of the efficiency frontier can be shown as a function of the varied parameter. In probabilistic sensitivity analyses, for example, the cumulative distribution of the target parameter can be presented or the results can be presented graphically in scatter plots. If a probabilistic sensitivity analysis is to be carried out for the entire efficiency frontier, confidence bands can be shown. It should be noted that health effects and costs can be connected (e.g. reduced costs by shortened hospital stays, which in turn result from more effective therapy), and this must be taken into account in the model and in the Monte Carlo simulation. Moreover, the dominant behaviour should be considered when calculating confidence bands. Thus, different interventions can be dominated in separate Monte Carlo simulation runs which means that the efficiency frontiers generated can each consist of different interventions. From this, 95 % confidence intervals for the last (far right) gradient of the efficiency frontier, for example, can be derived.

When presenting the results of the sensitivity analyses, care should be taken that the variation of certain parameters can influence the position of the efficiency frontier. With respect to a deterministic sensitivity analysis, parameter values should be identified, for which the new technology is cost-saving, or is above or below the efficiency frontier. For the probabilistic sensitivity analysis, the proportion of simulations generating cost-savings or leading to a position above or below the efficiency frontier should be provided.

CHAPTER 6

6 Efficiency frontier concept

6.1 Introduction

The method for comparative health economic evaluations presented here meets the requirements imposed by the German context (see Section 1.1 General conditions) while remaining consistent with the theory underlying the predominant methods used in this field. This is achieved by modifying the established efficiency frontier approach.

6.2 Efficiency frontier

Approach:

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

Combination therapies are also included among the health technologies to be assessed. Depending on the type of combination therapy, these need to be treated differently in the health economic evaluation. Fixed and free combinations are differentiated between, i.e. a prescription for a fixed combination and that for a possible combination. The benefit assessment of a fixed combination is simpler and predominant. A procedure for these special cases is given in the preliminary report plans.

6.2.1 Rationale

In health economics, the efficiency frontier concept is an extension of the standard approach of incremental cost-effectiveness ratios. The method specifically enables the consideration of the rational use of resources within a single therapeutic area, while retaining the results of the benefit assessment by IQWiG and hence avoiding discrimination.

The efficiency frontier provides information which can serve as guidance for decision makers with regard to setting maximum reimbursable prices, while being consistent with basic economic principles. Without employing a universal threshold – which is currently non-existent in Germany – the efficiency frontier method is based on the determination of the prevailing efficiency in a given therapeutic area in Germany. The efficiency frontier itself is comprised of the most efficient therapeutic alternatives within the particular therapeutic area. Recommended actions for the decision maker can be derived from the last plotted point on the efficiency frontier (technology showing the highest benefit).

6.2.2 Definition

The efficiency frontier plot compares the therapeutic benefit of available interventions within a given therapeutic area with the outcome-related net costs of these interventions. The additional therapeutic benefit derived from a previous benefit assessment may be transferred into an approximately cardinally scaled measure.[2] Interventions on the efficiency frontier denote the net cost for any given benefit that is consistent with the efficiency that can be achieved by the package of interventions on the current market. Prices can lead to health technologies being positioned on an already existing segment of the efficiency frontier, showing thereby consistent efficiency with already existing interventions. If a price results in an intervention being positioned below the efficiency frontier, this indicates a lower efficiency. This price is deemed too high and needs to be adjusted, or at least justified. Interventions above the efficiency frontier indicate improved efficiency and thus redefine the frontier.

6.2.3 Procedure

As demonstrated, the health economic evaluation of an intervention that displays additional benefit compared to the comparator in the benefit assessment forms the basis for recommending the setting of a maximum reimbursable price. This intervention can be an innovation or an existing relevant intervention. The evaluation, on the one hand, of technologies that are incorporated into determining the efficiency frontier and, on the other, of the technology for which a maximum reimbursable price has to be determined must be differentiated in the procedure: firstly, for determining the efficiency frontier and, secondly, the recommendation that can be derived from it for setting a maximum reimbursable price. The first are those technologies that are currently used in Germany for the indication area awaiting assessment. Their costs and benefit have been obtained and are depicted diagrammatically. If the result is plotted according to the benefit assessment of these technologies, it would be as in Figure 4, with the new technology not yet included.

[2] If the additional patient-relevant benefit, assessed by means of the prior benefit assessment, already shows approximately cardinally scaled characteristics, it may be directly transferred into the cost-benefit assessment

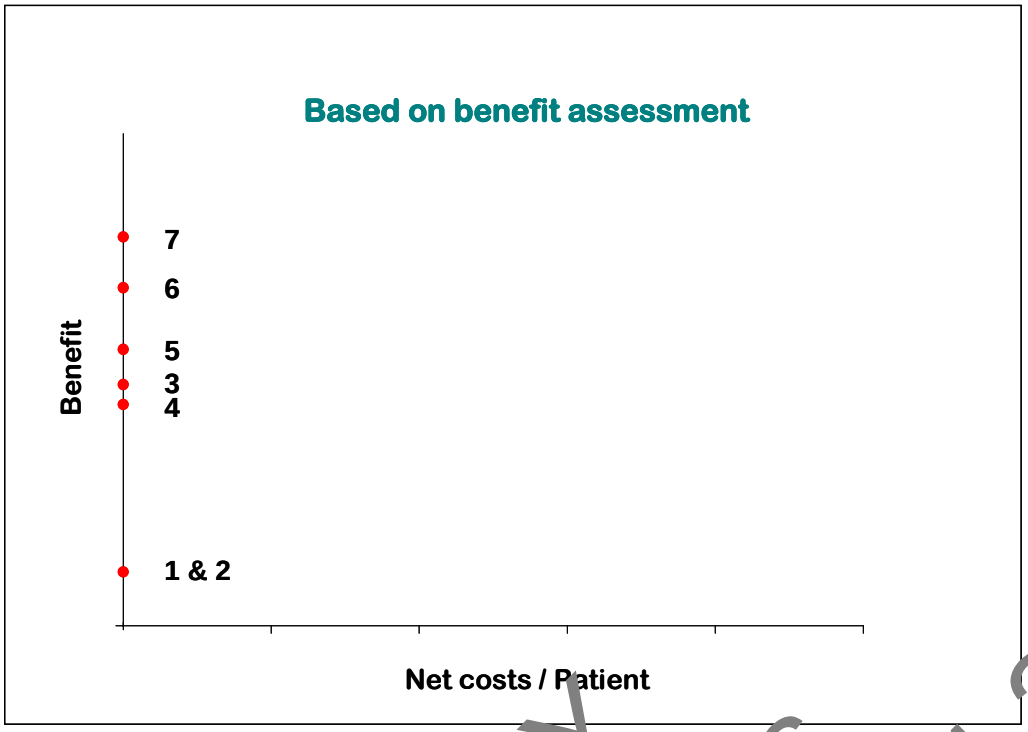

Figure 4: Results based on the benefit assessment

In the second step only, as shown in Figure 5, the benefit and costs of each of the comparators are plotted on the cost-benefit plane.

6.2.4 Concept

The theoretical efficiency frontier plot shows options increasing in efficiency from left to right. The gradient of the line segment connecting any two options represents the incremental benefit per incremental net costs (Figure 5).

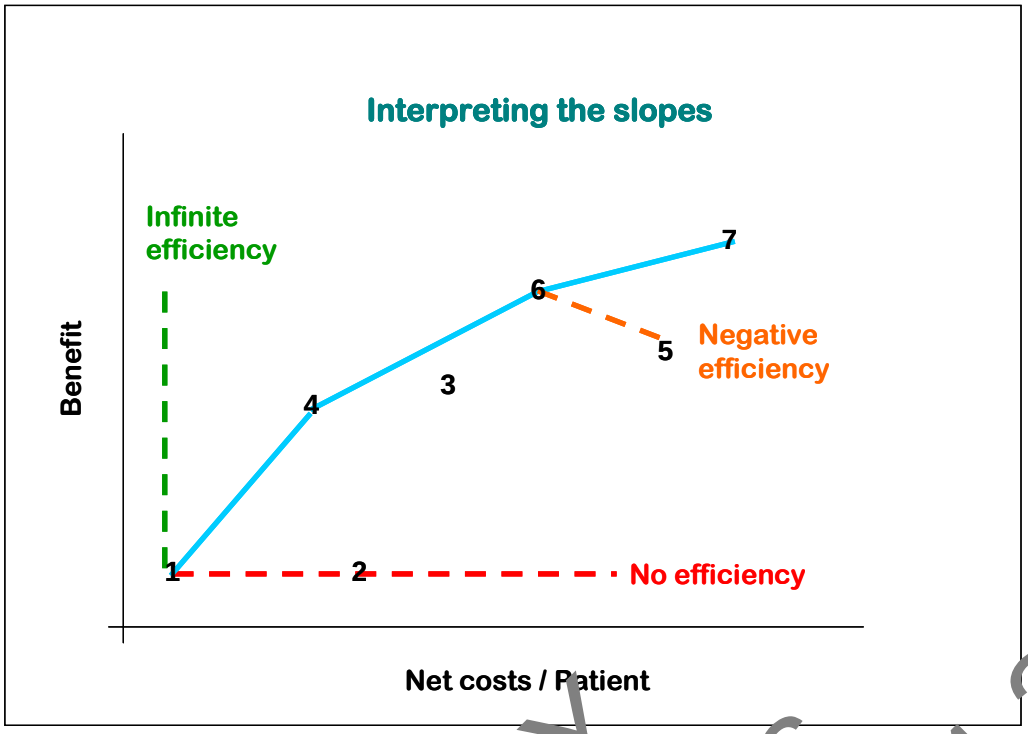

Figure 5: Interpreting the slopes of the theoretical efficiency frontier

The horizontal gradient (= 0°) indicates no efficiency (e.g. 2 versus 1) while the vertical gradient (= 90°) indicates infinite efficiency. Positive gradients (e.g. between points 6 and 7) reflect additional benefit for increased cost, while negative gradients (e.g. between points 6 and 5) indicate less benefit yet more costs.

The positions of interventions such as Intervention 3 in Figure 5 require further interpretation, as they do not reflect negative efficiency with respect to any existing intervention (e.g. Intervention 4). In Figure 6, 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 show negative efficiency (higher costs with less benefit) with respect to at least one existing intervention on the theoretical efficiency frontier. Options in these areas (e.g. 2 or 5 in Figure 6) are clearly inefficient. This leaves triangular areas E, F and G, where options are not wholly inefficient. Generally, options plotted 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 benefit for lower costs ("extended dominance").

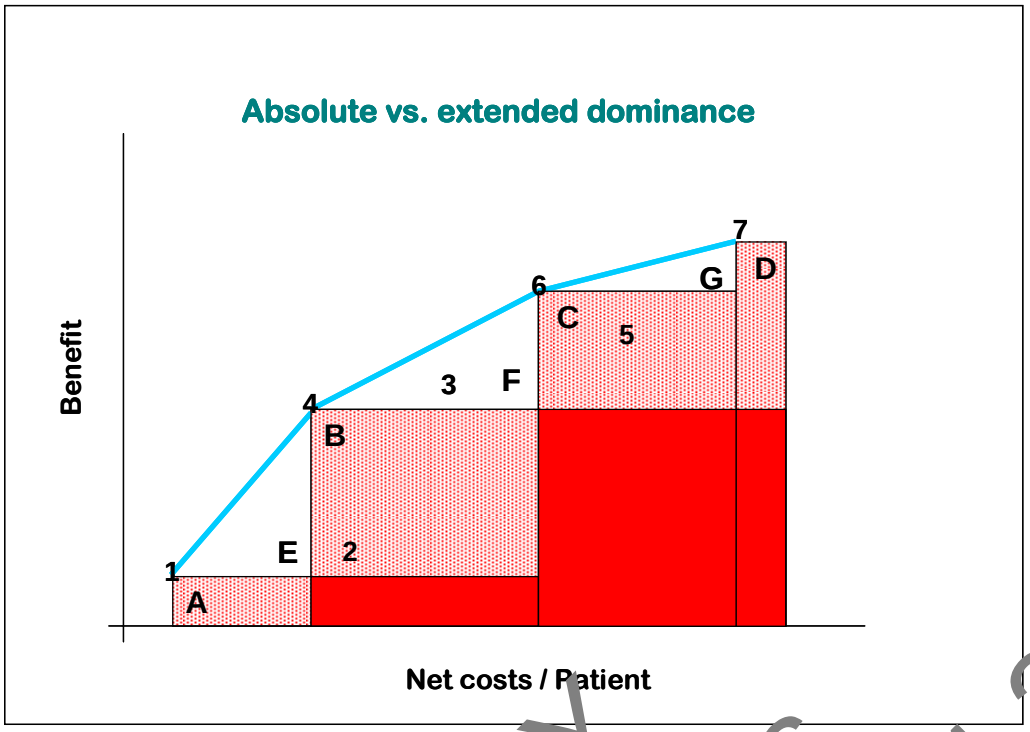

Figure 6: Absolute versus extended dominance

The theoretical efficiency frontier (solid line) joins those points that are efficient relative to any other option or combination of options. These options demarcate rectangles A-D and any options in those areas (e.g. 2 or 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 might be possible, this is not always the case. It implies, for example, that if the price of option 3 is fixed, then its beneficiaries would need to be redistributed to 4 and 6 to achieve greater efficiency. This may be clinically undesirable and may be difficult to justify, since it would lead to those receiving option 4 being in a worse position. The alternative of allowing beneficiaries to alternate between the two therapies over time is clearly not possible with most surgical, and presumably not with many drug interventions either. Thus, there may be many situations where options in the triangles constitute part of the practical efficiency frontier. If extended dominance is not considered, then a stepped, absolute efficiency frontier is provided by joining the upper segments of the lightly shaded rectangles as opposed to the heavily shaded rectangles.

6.2.5 Time horizon

In principle, the health economic evaluation should cover the duration of the randomized controlled trials and, as a secondary scenario, be extended beyond this time period if this is relevant for the decision maker. The time horizon should appropriately reflect the natural course of a disease and be sufficiently long to capture all relevant benefit and cost considerations related to the health technology or programme [52]. In addition, all selected

technologies should be assessed over the same time period. Most clinical trials measure the benefit over much shorter periods than justified by the characteristics of the disease. For many chronic diseases, this time horizon corresponds to the patient's life expectancy. The time horizon for cost estimation need not be limited to the periods for which there is evidence from clinical trials for a benefit from health technologies. However, prognostic adjustments should not artificially generate "new health benefits". The results of the assessment for periods of time for which studies have been carried out (primary scenario) and the periods of time extending beyond this (secondary scenario) are reported separately. The choice of time horizon must be carefully documented and justified in the light of the specifics of the therapeutic area and health technologies.

6.2.6 Discounting

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

Discounting of benefits can be carried out according to the method used for cost estimation.

The choice of discounting rate has a significant effect on the results of the health economic evaluation. Although various rates are given in health technology assessment guidelines [53-56], a discounting rate amounting to 3 % is stipulated based on the present international long-term equity market costs [57]. Sensitivity analyses have to be performed in order to examine the robustness of the results compared to the variation of this cost factor. These sensitivity analyses should be conducted for discount rates of 0 %, 5 %, 7 % and 10 %.

6.3 Constructing the efficiency frontier

Approach:

The efficiency frontier plot is designed in such a way that it represents the relevant health technologies in a given therapeutic area. This involves:

- **Full, detailed specification of the therapeutic area in question. This may include the specific disease, the conditions of treatment (e.g. inpatient care), target population, ranking of therapy (first, second choice, etc.), and whether it is a mono-therapy or combination therapy.**

- **Scoring existing therapies on the basis of benefits and costs.**

- **Entering therapies on a coordinate system with the benefit on the vertical axis and costs on the horizontal.[3]**

- **Drawing the efficiency frontier.**

Evaluation of new health technologies for setting maximum reimbursable prices in Germany should be carried out in the context of the relevant efficiency frontier. It records the health effects and costs of the new intervention already available in the intended therapeutic area.

In order to construct the frontier there are three major steps to take:

- Define the vertical axis, quantify the benefit for the chosen interventions and ensure an approximately cardinal scale is used which reflects the benefit in the therapeutic area in question.

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

- Plot the interventions and draw the efficiency frontier.

6.3.1 Vertical axis

Approach:

- **The vertical axis reflects the benefit assessed by IQWiG.**

- **The benefit is parameterized on the basis of patient-relevant outcomes (which may also include quality of life scores, or integrative scores for health consequences), or on the basis of responder measures.**

- **The benefit is transferred to the vertical axis after transformation, if applicable, into an approximately cardinally scaled measurement. This transformation may be performed using modelling to take into account prolonged time horizons or national health care aspects.**

- **In the case of patient-relevant additional benefit, depending on the number of outcomes for which a patient-relevant additional benefit was shown in the previous benefit assessment, multiple efficiency frontiers may be derived and can be presented to the decision maker.[4] If outcome weighting is carried out, this should also be presented to the decision maker.**

[3] Tabular representation is also possible, although the relationships are not as apparent.
[4] This also refers to the separate diagram on divergent harm aspects bordering patient-relevant additional benefit.

6.3.2 Horizontal axis

Approach:

- **Total net costs per patient are plotted[5] on the horizontal axis.**
- **Generally the costs are estimated from the perspective of the community of SHI insurants. They may contain additional costs arising from extended perspectives, depending on the commission (e.g. social insurance perspective, societal perspective).**
- **The time horizon should be sufficient to cover the majority of relevant costs.[6]**
- **The costs should be those that are expected to accrue at the current time.**

Cost operationalization

In order to estimate the costs of each intervention and plot them on the efficiency frontier graph, several conditions must be met. The costs should be those that would be incurred in current practice. They should be represented on the efficiency frontier plot in terms of the total net cost per patient treated since these are easier to estimate and understand.

6.3.3 Plotting the efficiency frontier

The first segment of the theoretical efficiency frontier ranges from the no-intervention point to the intervention with the best cost-effectiveness ratio, in other words, the one that produces the most benefit per unit cost (i.e. the steepest positive gradient). This will often be the least expensive intervention, but may occasionally be another one that, although more expensive, provides even more benefit per unit cost. The correct choice can be determined graphically by sweeping a clockwise radius from the vertical axis clockwise until it encounters a plotted intervention. That will be the first point on the efficiency frontier (see Figure 7).

[5] They can also be represented as a table.

[6] This may pose some difficulty if there is a discrepancy with the time horizon that was used for the benefit estimation. If this occurs, modelling techniques must be applied to resolve the discrepancy. Results arising from health economic evaluations over time horizons for which there are study results are to be reported separately.

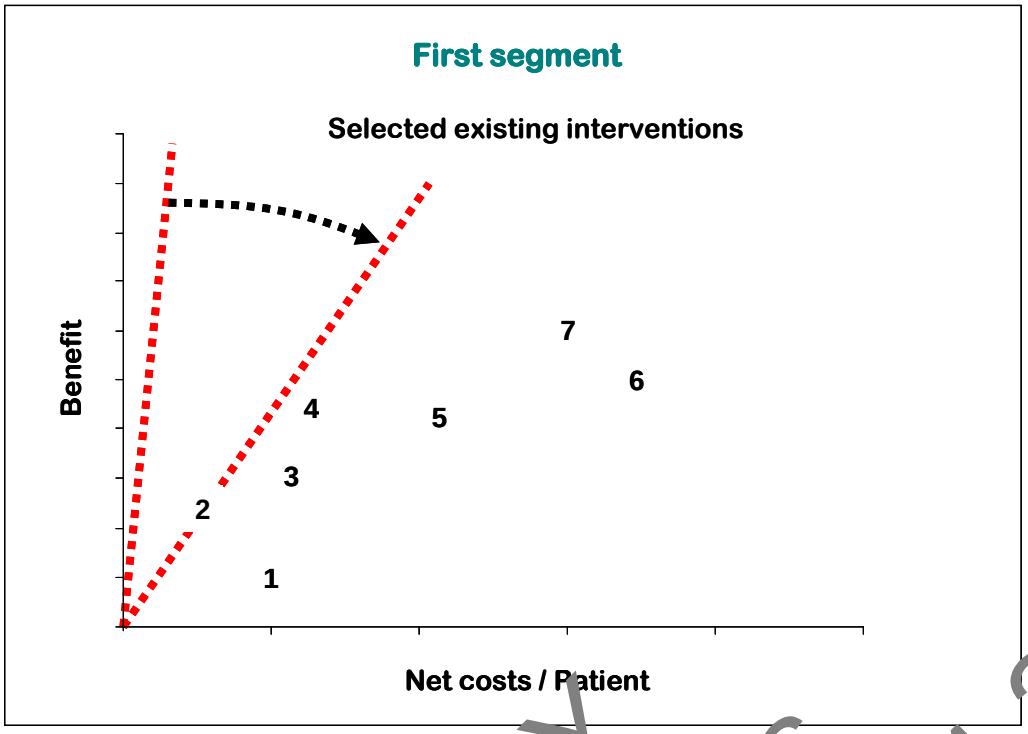

Figure 7: First segment

Selecting the first point on the theoretical efficiency frontier. The figure illustrates the clockwise sweeping of a radius from the vertical axis until it reaches a plotted intervention; point 2 is thus the first point on the theoretical efficiency frontier.

The no-intervention point also requires some assessment. Although it might be taken to be the coordinate origin (zero benefit and zero costs), this is rarely appropriate as the absence of intervention may still produce costs and health effects due to the untreated illness, monitoring, etc. This can be taken into account by shifting the axes so that "no intervention" is the coordinate origin (Figure 8). This simply involves subtracting the no-intervention amounts from the benefit and corresponding costs of the selected health technologies.

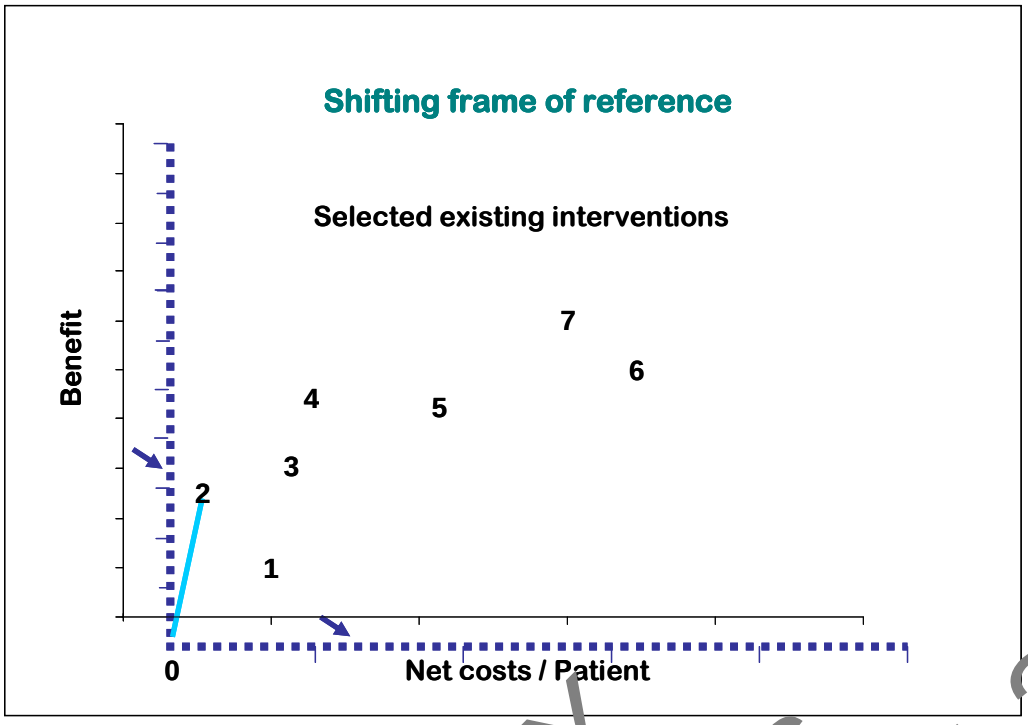

Figure 8: Shifting the frame of reference

Shifting the coordinate system to determine 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 coordinate origin to the first intervention identified by the clockwise sweeping radius.

After the first intervention is plotted on the theoretical efficiency frontier, the remaining health technologies are assessed in order of increasing cost to determine whether they provide more benefit than the first one. Among those that do, the one with the next highest estimated benefit per unit cost (i.e. with the highest remaining gradient 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 reaches the next intervention.

In this case any new intervention would be considered with reference to the efficiency frontier.

6.4 Specific situations

Two situations can occur, in which no recommendation can be derived for an innovative health technology based on an efficiency frontier approach. Both situations seem to occur very rarely in practice.

1) The last technology on the efficiency frontier (before the new technology was introduced) dominates all other technologies and generates the same cost as the reference scenario. The gradient of the efficiency frontier would be infinite.

2) The last technology on the efficiency frontier (before the new technology was introduced) is cost-saving and more effective than all comparators, including the reference scenario.

Based on the method of constructing an efficiency frontier, as laid down in this methods paper, both cases would result in a new zero point, created by the last technology before the introduction of the innovative technology. In these circumstances, the budget impact analysis might deliver further information. The decision maker could also, as with all other recommendations given by IQWiG, use other criteria to decide on a maximum reimbursable price for a technology. In addition, all efficiency frontiers constructed in a therapeutic area should be provided, so that the decision maker can take into account all comparators dominated by the last technology when making a decision concerning the evaluation of new technology.

CHAPTER 7

7 Recommendations

7.1 Appropriateness of costs

The main purpose of the health economic evaluation is to facilitate decision making with regard to setting a maximum reimbursable price by presenting key information derived from health economic evaluations. This does not prevent decision makers from considering other factors in the ultimate decision-making process. The Institute's recommendation therefore refers to deriving an appropriate maximum reimbursable price for the measure to be evaluated from the average net costs per patient. The maximum reimbursable price is based on the cost effectiveness ratios on the efficiency frontier.

The points on the efficiency frontier indicate the net cost at which a given level of benefit is being provided in Germany at that time. They illustrate the potential achievement of benefit in that therapeutic area. The efficency frontier denotes the relation between net costs and the benefit which is consistent with the efficiency of available interventions. If prices position an intervention to the right of the efficiency frontier, this indicates a lower efficiency and thus requires particular justification (see Figure 9). The efficiency frontier itself allows decision makers to examine the existing interventions in relation to each other and to assess the efficiency of individual components in health care in a given therapeutic area.

Decision makers may choose to use this efficiency frontier as guidance in two ways: on the one hand, they may infer that a new therapy which lies above the existing maximum benefit level should be reimbursed by an amount that is consistent with the previous efficiency, unless documentation to the contrary is given. On the other hand, if the price is such that the therapy is more efficient compared to the efficiency of the given comparators with the greatest benefit in this therapeutic area, there will be less reason to dispute the price.

The efficiency frontier also clearly shows outcome-related inefficient interventions (e.g. those that are both more costly and with regard to an outcome, of less benefit than other existing options). In principle, questions may be raised as to whether the prices of such options need to be reduced if they are to continue to be covered fully by the SHI, or if these alternatives should be excluded from reimbursement. All those points below the efficiency frontier are outcome-related inefficient and consequently also uneconomic. General guidance for such points, depending on the relevance of the individual outcome, is that their cost is considered too high and should be reduced to the level shown by the efficiency frontier, if possible.

If both the costs and the benefit produced by the new intervention are higher than those already within the efficiency frontier, the costs that are appropriate for this intervention cannot be derived from the frontier itself. Thus, additional criteria have to be considered to assess whether using an efficient but more costly new therapy method is an adequate measure.

The Institute assumes that a deterioration in efficiency of health care caused by adopting a new medical procedure is not appropriate. Therefore, with a given benefit from a measure to be evaluated, those prices are deemed appropriate that do not lead to a deterioration of efficiency in a given therapeutic area measured against the efficiency frontier (see Figure 9). The recommendation of the Institute will therefore designate a price which does not result in a deterioration of efficiency within the given therapeutic area.

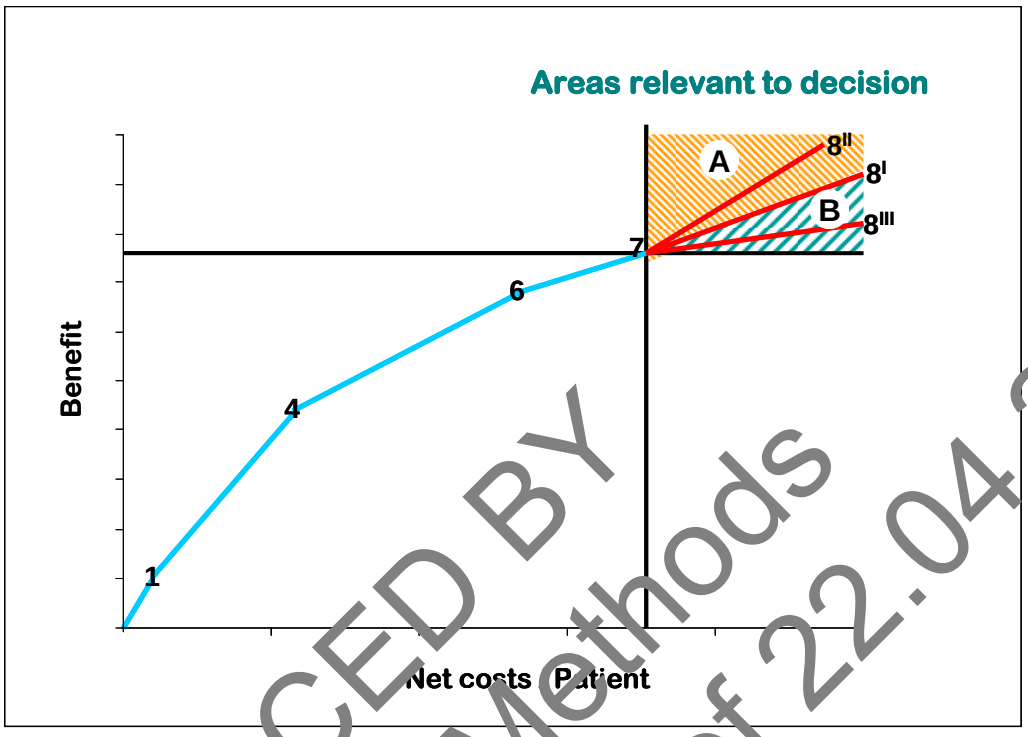

Figure 9: Areas relevant to decision making

Interventions located according to outcome on the shaded section A (8'') reveal a greater benefit in relation to costs than the existing benefit obtained for the indication under consideration. The costs indicated should therefore be reimbursed. Interventions on the shaded section B (8''') reveal a lesser benefit for the costs indicated, so their price should not be considered appropriate. Taking into consideration the criterion of appropriate costs, the decision maker can fix a maximum reimbursable price. Interventions with an unchanged cost to benefit relation (8') also meet the criterion of appropriate costs.

If it is necessary to determine several efficiency frontiers to assess an intervention, the price of an intervention is considered appropriate – observing the relevance of patient-relevant outcomes – if it does not lead to a deterioration of efficiency in the efficiency frontier with the lowest efficiency. The decision rests with the decision maker as to whether or not to take into account the results of any prior outcome weighting when setting a maximum reimbursable price. A similar approach can also be considered when a drug is approved for several therapeutic areas.

7.2 Reasonableness of the coverage of costs

The Institute assumes that the reasonableness of the coverage of costs by insurants in Germany depends on the one hand on the appropriateness of prices for a medical intervention. On the other hand, it also depends on the estimated future total expenditure, and the financial capacity and willingness to pay of the insurants. Since neither the insurants' financial capacity nor their willingness to pay can be measured, the Institute is unable to make precise recommendations on the reasonableness for cost coverage. However, the Institute can assist this assessment by describing the possible future financial impact arising from this type of cost coverage. For this purpose IQWiG has performed a budget impact analysis. The detailed budget impact analysis for determining a possible expenditure rate on the basis of appropriate pricing/setting a maximum reimbursable price illustrated in Section 7.3 also includes a calculation of the potential efficiency reserves including scenarios which exclude certain therapies as well as adjust prices for dominant technologies.

7.3 Budget impact analysis

Even after a new health technology has gained a positive assessment in terms of benefit, and has been shown to be on or above the efficiency frontier, it must still be affordable to German insurants [58]. The assessment of this aspect requires an economic evaluation which investigates the impact on total expenditure of the previously determined appropriate maximum reimbursable price.

7.3.1 Definition

Budget impact analysis is an assessment of the direct financial consequences of reimbursing a health care technology in a specific health care setting [59]. It is complementary to the comparative health economic analyses that examine the cost-benefit relation of health technologies. Budget impact analysis uses scenarios to map the future financial impact. It does so by considering the potential number of patients receiving a new therapy, as well as the prevalence of the therapy in the health care system, including its use on previously untreated patients. In particular, a budget impact analysis 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 [60].

There may be circumstances where the health economic evaluation indicates an efficient technology, while the budget impact analysis indicates that its financing still represents a great burden. The decision maker needs to find a solution to this issue of reasonableness. In this regard, IQWiG will describe the possible financial impact but will not make concrete recommendations regarding the reasonableness of cost coverage.

7.3.2 Procedure

The purpose of a budget impact analysis is not so much to produce exact estimates of the financial consequences of a health technology but to provide a valid computing framework (of a model) that allows users to understand the relationship between the characteristics of their setting and the possible expenditure consequences of a new health technology (or of a change in usage of current health technologies) [60]. Such a model is required because many of the parameters vary depending on the constellation and there is uncertainty about them. Thus, there is not a single expenditure impact estimate but rather a range and it is this range that the model is designed to produce. Proper design of the analytical framework is a crucial step in the budget impact analysis.

This section provides an overview of the most important components of the analytical framework for the budget impact analysis.

7.3.2.1 Perspective

Approach:

The budget impact analysis should be undertaken from the perspective of the budget holder.

The budget impact analysis should be undertaken from the perspective of the SHI or another relevant budget holder. Any expenses incurred or savings achieved outside of this perspective are not included.

7.3.2.2 Scenarios

Approach:

The budget impact analysis should compare health care scenarios, not individual health technologies.

A budget impact analysis compares health care scenarios, each defined by a set of health technologies – rather than specific individual technologies [60]. At least two scenarios must be considered. One is the reference scenario defined as the current mix of health technologies and the other is the predicted new mix of health technologies.

7.3.2.3 Population

Approach:

The likely number of insurants using the new health technology should be predicted. The model must allow for patient subgroups to be included

The size of the insured population likely to use the new technology is one of the key factors that determine the amount of the budget that will be spent on the new health technology. The projected number of actual users is derived from the predicted utilization of the health

technology within the target population. 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 [61]. In predicting the rate of users, both substitution of existing health technologies and induced demand need to be considered.

7.3.2.4 Time horizon

Approach:

The time horizon should be relevant to the budget holder.

The budget impact analysis should be presented for time horizons that are of most relevance to the budget holder in view of their expenses [60]. These time horizons are usually short term. Since the impact on expenditure is likely to change over time after the new health technology is introduced – both because of gradual market adjustment and long-term effects on the disease in question – these should be estimated and presented for at least two periods [62]. To be useful, the output must thus be the period-by-period level of expenses and savings rather than a single "net current value" [60]. Thus, no discounting of financial streams is applied.

7.3.2.5 Presentation

Costs should be estimated according to the methods outlined in chapter 4:

- **Results should be presented as a range rather than a point estimator.**
- **Results of the budget impact analysis should be presented both in terms of the total budget impact and as a fraction of the annual budget.**

Glossary

Additional benefit

In accordance with the Act to promote competition among the statutory health insurance funds (*GKV-Wettbewerbsstärkungsgesetz* [GKV-WSG 139a (3) SGB V]), IQWiG is commissioned to assess the benefit and cost of drugs. The type of benefit and cost assessment of drugs is explained in more detail in §35b (1) SGB V, whereby an assessment is carried out to determine any additional benefit to the patient in relation to cost by comparing different drugs and forms of treatment. Benefit or harm is established by comparison to a placebo (or another type of sham treatment) or to no treatment. When a medical intervention is evaluated in a comparison with another clearly defined medical intervention, IQWiG describes any greater benefit as "additional benefit" [8].

Benefit

The term "benefit" is used in both a broad and a narrow sense in health economic literature. In its narrow sense it is linked to EBM and reflects the pure medical benefit in evaluating an intervention (= health effects/outcomes). In its widest sense the term "benefit" not only includes the health effects of an intervention per se, but also the value that the patient ascribes to this effect (often also referred to as utilities). These utilities can be used to weight effects, thereby increasing or reducing the importance of an effect from the perspective of the persons concerned.

Diagnosis related groups (DRGs)

Predetermined payments according to diagnosis-related case groups with a fixed amount paid for inpatient stays. Depending on the severity and services rendered, the hospital case or stay is reimbursed by the patient's health insurance fund using a DRG [63].

Discounting

Procedure for calculating the current value of a future value. Different interventions, whose benefit and cost arise at different points in time, can be compared by discounting against each other [63,64].

Effect

An effect in clinical trials describes a partial aspect of the clinical and/or functional state of a patient following a specific intervention.

EQ-5D

Standardized instrument for measuring health-related quality of life using the following five dimensions: mobility, self-care, usual activity, pain/discomfort, anxiety/depression [65].

Evidence-based medicine

The term "evidence-based medicine" (EBM) describes the application of medical services that are not solely based on opinion and agreement but draw on "evidence" characterized by proof that has been assessed using the most objective scientific methods. EBM comprises tools and strategies that are designed to prevent misdiagnosis and false hopes [8].

Federal Joint Committee (G-BA)

The Federal Joint Committee (Gemeinsamer Bundesausschuss) is the supreme decision-making body of the conjoint self-administration of physicians, dentists, psychotherapists, hospitals, and health care funds in Germany. For over 70 million insured members, it specifies the benefits catalogue of the statutory health insurance (SHI) funds by means of directives, and thus determines which health care services are reimbursed by the SHI funds. In addition, this Committee decides on quality assurance measures for inpatient and outpatient health care sectors [67].

Friction cost approach

The friction cost approach is used to measure productivity losses. It takes account of the time until a vacant position is filled again in estimating productivity losses due to illness. This period of time is known as the friction period [66].

GKV – National association of statutory health insurance funds

The central body representing the interests nationwide of the statutory health insurance funds (GKV) to which all health insurance funds belong. It represents the statutory health insurance funds in all legal matters where unanimous joint decisions must be agreed [68].

Head-to-head comparisons

Direct comparative trials where two or more (approved) drugs or other health technologies for a therapeutic area are compared with each other.

Health utility index (HUI)

Standardized one-dimensional index value for measuring health-related quality of life; its algorithm is based on preferences of the Canadian population [69].

Human capital approach

The human capital approach is used to measure productivity losses. It valuates the loss in production when calculating the indirect costs from the expected future earnings. In estimating the loss, it is not taken into account whether the work can be taken on by someone else if a person falls sick or dies [66].

Marginal willingness to pay

Payment that the provider or patient is willing to pay for an additional benefit unit gained through a new health technology in a therapeutic area.

Maximum reimbursable price

The amount up to which drugs that have a proven patient-relevant therapeutic additional benefit and are not allocated to a fixed-amount group are reimbursed by the GKV. The GKV-Spitzenverband lays down the maximum amount for each drug. This may also be done with the agreement of the pharmaceutical companies. An IQWiG cost-benefit assessment can be the basis for establishing a maximum reimbursable price [1].

Meta-analysis

In a systematic review, a meta-analysis is a statistical technique used to summarize quantitatively the results of several studies on the same question into an overall result. This increases the evidential value (certainty of results) compared with an individual study [67].

Model/modelling

There are various definitions for the term "model" in the context of health care. Models are analytical tools used to understand systems in the real world, estimate various outcomes in relation to a given set of input parameters, and model the effects of changes on the system. Models should be interpreted as a portrayal of reality consisting of a reduced set of components and requiring simplifying assumptions. The validity of a model depends definitively on whether the system thus represented is adequately reflected. For periods of time where there is no proof of cost or benefit from studies, data from primary or secondary sources are simulated by means of different mathematical techniques in modelling. Modelling can also be used to transfer study results that are out of context to a specific national context.

Off-label use

Use of a drug for applications not approved by the authorization bodies [63].

Opportunity costs

Societal value that the resources utilized in a technology would have in an alternative use. The basic idea is that each monetary unit can only be used once and a decision on a medical intervention always means that another service is forgone.

Outcomes

- An outcome is an effect that can be ascribed to a specific intervention, i.e. this assumes a causal relationship between intervention and effect (= outcome). Outcomes are measured in order to estimate the effectiveness/efficacy of an intervention.

- Disease or treatment related changes can be measured according to different outcomes. Outcomes are, for example, mortality, morbidity, and health-related quality of life. An outcome usually includes different outcomes. For example, the mortality outcome can include "all-cause mortality" and "mortality caused by coronary heart disease". Morbidity can include "non-fatal heart attack" and "adverse events".

Outcomes, continuous

An outcome that is measured on a continuous scale. Blood pressure is an example of a continuous outcome.

Outcomes, dichotomous (binary)

An event that either occurs or does not occur in patients. For example, participants of a study may either experience a heart attack or not, or they may survive or not. The term serves to distinguish from the term "continuous outcome".

Patient-relevant outcome

In the benefit assessment, benefit is described as a causal positive effect, harm as a causal negative effect of a medical intervention, with reference to patient-relevant outcomes. Patient-relevant in this context refers to a patient's subjective wellbeing, how they cope with everyday activities from a subjective viewpoint and whether they survive. Outcomes that are reliable and depict direct concrete changes in the health state are considered first of all, for example, all-cause mortality and heart attacks (see also "outcomes") [8].

Person trade-off

Method for assessing the societal value of various medical interventions. The respondent decides between two different sized groups of people, in one group there are x persons in health state A, and in the other group y persons in health state B. However, only one group may receive help. The number of persons in the groups is then altered until both options are considered equivalent by the respondent [107].

QALY (quality-adjusted life year)

A benefit concept based on the expected utility theory, in which gained or expected life years and the change in quality of life expressed in utilities (health-related) are merged in an index. Each health state is given its own utility documented from patients or other reference populations. The QALYs of an individual are estimated by weighting the expected duration of each health state with the utility of this state. The QALY ranges from 1 to 0, whereby a QALY of 1 indicates one year of full health and a QALY of 0 corresponds to death. The gain in QALYs from an intervention corresponds to the benefit.

Quality of life score

One-dimensional result value that is the product of the summary of different dimensions when measuring quality of life using standardized as well as specific instruments. These dimensions do not need to be equally weighted.

Sensitivity analysis

A sensitivity analysis is a technique used to determine how sensitively a model calculation or a meta-analysis reacts to changes in methodology (e.g. when individual studies are excluded from the analysis) [67].

Standard gamble

Method for directly obtaining respondents' preferences for health states so that QALYs can be determined. Subjects are asked to imagine a hypothetical scenario where they are placed in a particular health state on account of a disease. A potential treatment could fully cure them with the probability p, or lead to immediate death with the probability (1 − p). In order to define the preference for the health state, the probability p of the respondents' indifference to either option is elicited [71].

Surrogate parameters (intermediate outcome)

Outcomes not of immediate relevance to patients, but associated with patient-relevant outcomes (for example, reduction in blood pressure as a surrogate outcome for the prevention of a stroke). Surrogate outcomes are often physiological and biochemical parameters that can be measured relatively quickly and easily. Surrogate parameters are often used if patient-relevant outcomes occur rather infrequently or only after a long period of time.

Even if a surrogate parameter is associated with a patient-relevant outcome, it does not mean that a causal relationship necessarily exists between the two. As long as a causal relationship has not been explicitly demonstrated, changes in a patient-relevant outcome cannot be inferred from changes in a surrogate parameter [67].

Time trade-off

Method for directly obtaining respondents' preferences for health states so that QALYs can be determined. Subjects are to imagine a hypothetical scenario where they are placed in a particular health state on account of a disease. A treatment could fully cure them but they would have to accept a shorter lifespan. The number of lost years the respondents are indifferent to indicates their preferred health state [71].

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