Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Institute for Quality and Efficiency in Health Care

Working Paper
Cost Estimation

Version 1.0 – 19/11/2009

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List of abbreviations

AG MEG	Arbeitsgruppe Methoden der gesundheitsökonomischen Evaluation (Working Group on Methods in Health Economic Evaluation)
DGSMP	Deutsche Gesellschaft für Sozialmedizin und Prävention (German Association for Social Medicine and Prevention)
DRG	Diagnosis Related Group
EBM	Einheitlicher Bewertungsmaßstab (Doctors' Fee Scale [reimbursement catalogue for outpatient sector] within the Statutory Health Insurance Scheme)
GOÄ	Gebührenordnung für Ärzte (Medical Fee Schedule for Care outside the Statutory Health Insurance Scheme)
HUI	Health Utility Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
QALY	Quality Adjusted Life Year
R&D	Research & Development
RCT	Randomized Controlled Trial
SGB	Sozialgesetzbuch (Social Code Book)
SHI	Statutory Health Insurance

1 The basics of cost estimation in health economic evaluations

1.1 Introduction

The result of health economic evaluations depends on the estimation of costs after the benefit assessment has been carried out. The current working paper, entitled "Cost Estimation" Version 1.0, has an introductory section outlining the basic principles of cost estimation, i.e. selecting the perspective for a health economic evaluation, the cost allocation and the definition of the different types of costs. Section 2 explains cost estimation step by step, i.e. identifying and quantifying the consumption and evaluation of resources. Sections 3 and 4 give a detailed description of the features of perspectives chosen that have a considerable influence on the results of health economic evaluations. The final section of this working paper comprises a list of potential data sources for health economic evaluations.

1.2 Perspective

Health economic evaluation studies can be carried out from different perspectives [1-8]. The perspective of a health economic analysis determines the entire process of cost estimation, i.e. not only the identification of the relevant resource consumption (expenditure or opportunity costs from a specific perspective), but also the quantification and valuation of the identified resource consumption (see Sections 2 to 5).

The perspective of a health economic evaluation is chosen according to the specific research question. A sample chart presenting possible perspectives is shown in Table 1.

The societal perspective is the broadest perspective. All costs are included, regardless of who will incur them: statutory health insurance (SHI), other social insurance schemes, patients and their families (e.g. time and travel expenses) or, for example, employers (e.g. productivity losses). The perspective of social insurance schemes considers only the costs directly involved, in other words, not the costs that the SHI insurants have to pay themselves nor any indirect costs resulting from productivity losses.

According to § 35b of Social Code Book V (SGB V), a health economic evaluation should be carried out as defined from the perspective of the SHI insurants. According to this perspective, the health economic evaluation includes both the disease-related services covered by the SHI, which must also be considered from a purely SHI perspective, and all costs that have to be borne by the insured individual.

In contrast, an exclusive SHI perspective only considers reimbursable direct costs and transfer payments.

Depending on the commission, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) will select the perspective

or perspectives for the health economic evaluation. Furthermore, this decision is linked to the relevance of the costs for the assessment of the particular health technology under commission. The chosen perspective could extend beyond that of the SHI insurants and include other social insurance providers (e.g. long-term care insurance, statutory pension insurance), but could also be the societal perspective that also integrates productivity losses on the cost side (in the form of indirect costs).

Cost category / **Perspective**	direct reimbursable medical costs	direct non-reimbursable medical costs	direct non-medical costs	costs of other social insurance schemes	transfer payments	indirect costs
society	x	x	x	x		x
social insurance	x			x	x	
SHI insurants	x	x	x			
SHI	x				x	

Table 1: Perspectives[1]

1.3 Allocation of costs

1.3.1 Direct and indirect costs

Costs in health economic evaluations are commonly classified into the following cost categories [4-6,8-11]:

- direct medical costs (or direct health care costs)
- direct non-medical costs (or direct non-health care costs), and
- indirect costs (or productivity losses)

Direct costs refer to the resource consumption in the provision of health care interventions. They encompass the entire current resource use and, depending on the timeframe under

[1] The precise resources to be included and to be calculated in each cost category may differ depending on the perspective taken.

consideration, also future resource use attributable to the programme. Future costs can span a lifetime in some therapeutic areas.

Direct costs are further split into direct medical and direct non-medical costs. Direct medical costs refer to the resource consumption in the health care sector associated with the provision of health care interventions. Resource consumption includes, for example, the costs of hospital stays, outpatient visits, drugs, medicinal substances and devices. Direct non-medical costs refer to resources supporting the medical services delivered in the health care sector. Depending on the perspective, these can be, for example, travel costs to medical interventions or the valuated time spent by patients and their family caregivers in relation to their illness.

Indirect costs denote the production losses due to

- incapacity for work (in the case of illness);
- occupational disability (in the case of long-term illness or disability);
- premature death.

Drummond et al. [9] suggested an alternative, pragmatic procedure to cost classification from the societal perspective: (1) resource use in the health care sector, (2) resource use in other sectors, (3) patient and family resources, (4) productivity losses. In this alternative classification, cost implications for other sectors (e.g. education in special schools for hearing-impaired children) are explicitly considered by separating non-medical costs into "resource consumption in other sectors" and "costs to those affected and their families".

1.3.2 Intangible costs

Intangible costs are a category of costs that is nowadays seldom used. These costs refer to items difficult to measure and value in cost terms, e.g. pain and suffering associated with a treatment. However, parts of intangible costs are actually not costs (i.e. no resources are denied an alternative use), and overall they are often not strictly intangible, as they can actually be valued through quality-of-life measures (through generic or disease-specific instruments to measure quality of life), or willingness-to-pay (an approach that will not be pursued in this technical document) [9]. In summary, intangible items should be reported on the benefit side.

1.3.3 Reimbursable versus non-reimbursable costs

The classification into reimbursable and non-reimbursable costs is perfectly suited to a combined SHI plus insurants' perspective in health economic evaluation. Reimbursable costs encompass in particular expenditure for necessary health care services and are covered by the SHI. Non-reimbursable costs are borne by the patients and their families. Non-insured costs to patients and their families are, for example, out-of-pocket expenses and co-payments for

drugs, medicinal substances, devices and outpatient consultations, and loss of net income due to illness.

1.4 Definition of types of costs

1.4.1 Marginal versus average costs

A basic decision in cost estimation is the choice of average costs or marginal costs [1,2,4,6,9]. Average costs are the costs per unit of output, marginal costs are the extra costs of producing one extra unit of output, i.e. one additional patient treated or one additional unit of intervention produced (see Table 2). One difference between the assessment of average costs and marginal costs is that fixed costs (such as buildings and equipment) are included in average costs, but are not considered in marginal costs. In health care there are scenarios where costs often increase more than proportionally when production output is expanded, and marginal costs will exceed average costs.

Which cost concept should be applied in cost estimation – average cost or marginal cost – depends on the specific research question. In general, health economic evaluation supports decision making on investment decisions (adoption of new technologies, licensing or coverage decision), which means that long-term costs (and effects) are relevant (in which all costs, including the short-term fixed costs, are variable). Moreover, the basic question in health economic evaluation concerns the additional costs (and effects) when output is slightly increased or decreased. Accordingly, the concept of long-term marginal cost is favoured in health economic evaluation.

Innovations and/or regulative changes may induce shifts of capacity utilization, i.e. a large decrease in demand (and capacity utilization) for some health care services and a large increase in demand (and capacity utilization) for others. Costs of adaptation to a new long-term equilibrium (with all short-termed fixed resources in a new optimal combination) are not usually calculated in health economic evaluation. Nevertheless, it is recommended that, if changes in (fixed) resource consumption are substantial, a qualitative description and a rough estimation of short-term costs and adaptation costs for the budget impact analysis is provided [6].

For the incremental cost approach, the difference in costs is obtained from the comparison of resource utilization between study groups and, therefore, depicts a difference between the average view of these groups. In the comparative health economic evaluation, the costs are shown per (average) patient. By contrast, in the analysis of impacts on health expenditure, the costs are calculated with regard to the patient group in question and are aggregated accordingly. Both the health effects obtained from clinical trials and the cost data determined from costs studies may be spread out, the latter to a greater extent. In this context, they are often right skewed cost distributions. When calculating average costs, this skew should possibly be statistically cleaned or taken into account in sensitivity analyses.

Total costs	TC	All costs relating to the production of a quantity of output q $TC(q) = FC + VC(q)$
Fixed costs	FC	Costs that are not dependent on output Example: building, equipment
Variable costs	VC	Costs that vary with the scale of production Example: personnel, material
Average costs	AC	Cost per output unit produced $AC(q) = TC(q) / q$
Marginal costs	MC	Extra costs associated with producing one extra unit $MC(q) = \Delta TC(q) / \Delta q$
Incremental costs	IC	Difference in costs between two technologies (difference) $IC_{AB} = TC_A - TC_B$

Table 2: Definition of costs
Source: based on Kristensen [12, p. 142]

1.4.2 Incremental costs

Incremental costs are another fundamental concept in health economic evaluation [1,5,9]. The difference between incremental costs and marginal costs is that incremental costs denote the cost difference between two alternative technologies, while marginal costs relate to the additional costs of producing an extra output unit of a technology.

Thus, in the incremental cost concept, two discrete alternatives are compared. This can involve two mutually exclusive procedures, for example, a drug and a surgical intervention relating to a given disease. However, the same intervention can be compared at different intensity levels (e.g. screening for colorectal cancer at different screening intervals). In the case of different intensity levels, no clear differentiation between incremental costs and marginal costs can be found in the literature. For example, in a multi-test screening programme for colorectal cancer [13], some authors apply the term marginal to costs of an additional test, while others use the term incremental [9,14]. According to the above definition, the example describes an incremental comparison. Incremental costs refer to the intervention options compared in health economic evaluation studies and comprise part of the core result of a health economic evaluation, the cost-effectiveness ratio.

1.4.3 Opportunity costs

Opportunity costs, too, are a basic theoretical cost concept in health economic evaluation [4,6,9,15]. They define the value of scarce resources in the production of health care interventions. Opportunity costs refer to the benefit of resources regarding the next best

alternative use of the resources. As is shown in micro-economic theory, opportunity costs are reflected in the market prices of a perfectly competitive market [15,16]. However, most markets in the health care sector are imperfect: prices are regulated by public institutions, or negotiated between associations of providers and health insurance funds, or do not even exist, which means that prices often are no adequate indicators of opportunity costs. Thus, for example, the prices of drugs, consisting of patented and off-patent drugs grouped together in jumbo groups, differ from the "actual" social opportunity costs.

1.5 Time horizon

The time frame should be long enough to capture the period of time covered by the studies and should be able to include cost and benefit differences relevant to the decision on reimbursement between the programmes compared in a health economic evaluation. For chronic conditions, a longer time horizon is possibly required (particularly if lifespan gains are expected) [4,5,8,9,17]. The time horizon in cost estimation must coincide with the time horizon in benefit estimation, so that a comparison of costs and benefit can be undertaken to obtain the cost to benefit ratio.

Often, the appropriate time horizon exceeds the time span of the available primary data from prospective studies because these are mostly undertaken over periods of time shorter than the natural course of a disease. In such cases, two time horizons should be investigated in health economic evaluations: an analysis that is based on study data from the benefit assessment and, if appropriate, a longer-term analysis that includes modelled data [5,10].

2 Process of cost estimation

Cost estimation is based on a four-step process:

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

In principle, all four steps could be integrated and total costs derived in a single step. However, the four-step process is recommended because executing separate steps is more likely to support comprehensive cost estimations [6] (although collecting cost data sometimes is easier than separating it into quantification of resource use and valuation of unit costs).

As mentioned in Section 1.2, the perspective of an economic evaluation determines the entire costing process. The general principles of cost estimation are described in more detail in the following sections. Chapters 3 and 4 deal with the particulars of cost estimation from different perspectives.

2.1 Identification of resource consumption

2.1.1 Methods for identifying resource use

A comprehensive identification of cost items relevant to the intervention options should be generated [4,8,9], even if not all cost items are finally quantified and valued, for example, because some cost items only have a minor impact on total costs, or on the cost difference (cost increments) between the intervention options.

The identification of the relevant resource inputs starts with the description of the production function of the health care intervention [4,6]. The production function combines knowledge of the intervention options, the natural course of the disease, impact of treatments on the disease (including productivity changes) and the interactions of patient subpopulations and the health care system.

Developing a decision tree of the therapeutic pathways which contains all relevant downstream events is recommended to ensure a broad identification of resources utilized. The decision tree should also include events not supported by the perspective investigated (for example, arising from rehabilitation treatment for employable persons from the SHI perspective).

Such events can involve resource consumption (outpatient check-ups to determine whether rehabilitation treatment has a sustained effect), which is then relevant from that perspective (in the SHI) [18]. Sources of information on relevant resources and production function will include [19]:

- studies and reviews of studies;
- textbook knowledge of the disease course and treatment alternatives;
- clinical practice guidelines;
- administrative and accounting data (e.g. data from all health insurance funds);
- expert opinions.

2.1.2 Intervention costs, follow-up costs and cost offsets

In health economic evaluations, a mere comparison of technology costs between new and existing health technologies is not sufficient. New technologies are frequently more cost-intensive than existing health technologies, which is particularly true for drugs.

However, in general, health interventions not only differ in mere technology costs, but also in their impact on (follow-up) costs for other health care services (and, of course, on benefit effects). Thus, the increased cost of a new technology may be offset by savings in other health care sectors. Cost offsets will be achieved when the new technology (e.g. new drug A) results in a cost reduction for other health care services (e.g. hospital stays and outpatient visits) compared to the alternative technology (e.g. existing drug B).

Therefore, as mentioned in Section 1.5, it is necessary for the time frame of health economic evaluations to be long enough to capture all relevant cost differences and benefit differences between the programmes compared in the health economic analysis. For chronic conditions, a longer time horizon might be required (particularly if the intervention is expected to produce lifespan gains).

Decision models can lead to cost savings if the clinical effects from randomized controlled trials (RCTs) are extrapolated together with supplementary information on resource consumption from other study types. These costs savings should undergo comprehensive sensitivity analyses as data generated by a model are less robust than data from studies.

2.1.3 Future costs (costs in life years gained)

In health economic literature, a differentiation is often suggested between

- related versus unrelated costs and

- costs in future life years under present treatment versus costs in life years gained [4,9,15].

Health economic guidelines agree that cost estimation can be limited to related costs (i.e. costs for diseases related to the intervention). Unrelated costs should be identical for all intervention options assessed in a health economic evaluation and therefore can be neglected in incremental cost-effectiveness analyses [4,9,15] as differences between treatment arms are distributed by accident. Ignoring unrelated costs will reduce estimation errors, but in practice this procedure rarely occurs. In the preliminary report plan, related and unrelated costs are differentiated according to case. Most authors agree that related costs in added life years (related future costs) should be included in health economic evaluations [4,9,15]. For example, if a cholesterol-lowering intervention extends lifespan, the costs of the lifelong medication (including treatment of side effects) and costs of cardiovascular diseases occurring during the life years gained will be included in the cost estimation. The inclusion of unrelated health care costs is more controversial [4,6,9,15]. On the one hand, future costs are a direct consequence of life-prolonging interventions. On the other hand, life-prolonging technologies (e.g. administration of drugs following a heart attack) are not linked to future therapeutic decisions (e.g. hip replacement).

Garber and Phelps [20] show that, under certain assumptions, the inclusion of unrelated cost does not change the ranking of incremental cost-effectiveness ratios (cost per life year gained). For all interventions, the cost per life year gained will increase by a fixed amount. Thus, if the (somewhat restrictive) assumptions of the Garber-Phelps model are accepted, the inclusion or exclusion of unrelated costs is unimportant. In contrast, Meltzer [21] argues (based on a less restrictive model) that all unrelated future costs, including impact on the individual's productivity and consumption, should be considered in health economic evaluations. Only then can decisions be consistent with lifetime benefit maximization.

Recently, the discussion has reignited as to whether future non-related costs should be included. As it is often difficult to allocate related costs, Rappange et al. [22] argue that internal and external consistency is only attained when all non-related costs are included in an analysis. In addition, they were able to prove that in various subgroups the cost-effectiveness relation can alter with the inclusion or exclusion of non-related costs.

Weinstein and Manning [23] indicate that both models adhere to the welfare economics approach and that a decision maker's approach, in contrast, leaves a greater degree of freedom in the analysis (allowing both inclusion or exclusion of unrelated costs). Similarly, most guidelines leave it up to the individual analyst, whether or not to include unrelated health care costs [4,9,18,24].

Summing up the controversial discussion on future costs, the following recommendations apply:

- Only future related costs should be considered in the base case.

- In sensitivity analyses, total health care costs (related and unrelated health care costs) in life years gained should also be calculated if possible.

2.2 Measuring of resource consumption: micro-costing versus macro-costing

In the literature, a range of costing approaches is applied with micro-costing and macro-costing defining the ends of the range [1,4,6,8,9,25]. In the macro-costing approach, composite intermediate products and services (e.g. inpatient days) are identified and measured. Micro-costing, on the other hand, starts with a detailed identification and measurement of services (e.g. a hospital stay split into components like consultation, operation, medication, diagnostics, nursing, accommodation, food, cleaning, overheads, etc.), and determines the required resource use (personnel, material, equipment, building, overheads etc.). For example, Figure 1 indicates the different precision grades of costing in hospital costing.

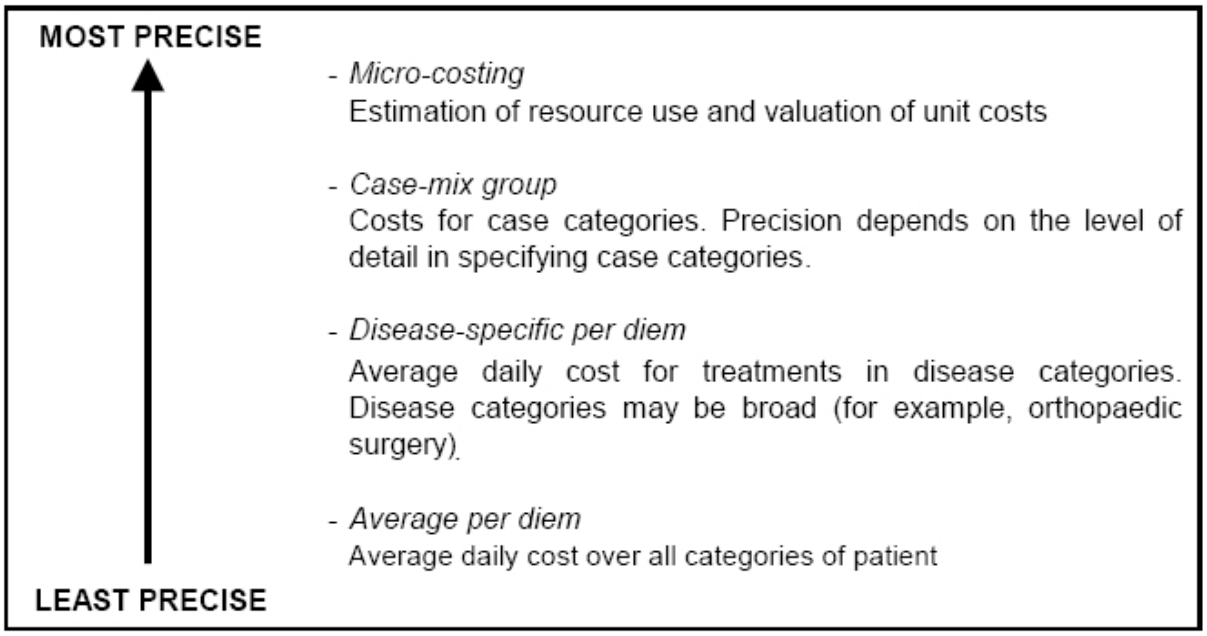

Figure 1: Grades of precision in hospital costing
Source: based on Drummond [9, p. 71]

The grade of precision to be applied in a health economic evaluation is an important criterion in selecting the approach. It determines the entire process of identification, quantification and valuation of resource consumption [4]. Factors influencing the required precision of cost estimations are:

- cost of products and services;

- frequency of utilization (or probability of occurrence): products and services that are cost-intensive and often utilized (by nearly all patients) should be measured using a micro-costing approach;
- point in time in the course of a chronic disease: for events in the distant future, macro-costing may be sufficient (due to the impact of discounting);
- variations between patients: when cost variations are small between patients, macro-costing may be sufficient (e.g. a hospital ward with relatively homogeneous services);
- variations between intervention options: similarly, when cost variations are small between concomitant and follow-up intervention, macro-costing will be sufficient [19].

Both costing approaches are often combined in a health economic evaluation: The micro-costing approach is used for resource consumption that is central to the health economic evaluation, whereas resources that are of less relevance to the disease and health services needed will be determined by the macro-costing approach [1]. In general, costs of the intervention options will be derived using a micro-costing approach.

An (often implicit) assumption in micro-costing is that the cost estimates (derived from one or several locations) are representative of the entire system [6]. This assumption should be verified. Macro-costing data are usually robust against geographical and institutional variations [6].

Again, as for the identification of resource consumption (see Section 2.1), a decision tree of the therapeutic pathways is useful to differentiate into central and less central cost items.

Sources of information on the required precision of cost estimations include [8,19]:

- studies and reviews of studies;
- clinical practice guidelines;
- administrative and accounting data (e.g. data from all health insurance funds);
- models (including combining data from various sources);
- expert opinions.

2.3 Resource valuation

2.3.1 Inflation adjustments and discounting

Health economic evaluation studies often require a long time horizon to capture all relevant cost and benefit differences between the programmes compared. Thus, costs accrue at different points in time over the course of a disease and health services utilization.

When price data utilized in health economic evaluations come from different time periods, adjustments to inflation should be performed. In principle, inflation rates specific to health care should be applied. As these specific inflation rates are not available for most health care services in Germany, it is recommended that the general price index (published by the Federal Statistical Office) is used.

There is a broad consensus in the literature that costs (and benefit) should be discounted to their present value to adjust for differential timing [9,26,27]. Discounting reflects the positive time preference of individuals, i.e. individuals prefer present to future benefit.

Reasons for a positive time preference are:

- diminishing marginal benefit of consumption, combined with expected increasing future income (assuming positive economic growth)
- risk of lifespan, i.e. risk of realizing future consumption.

As is shown in neoclassical theory, assuming perfect markets with accurate information about the future (i.e. no risk) and absence of taxation, the time preference rate will equal the market interest rate (i.e. the opportunity costs of capital), thus indicating the discount rate of society. Individuals will only forego present consumption if future consumption (based on investment) exceeds present consumption.

The proper discount rate is controversial. Often 3 or 5 % is suggested in international clinical practice guidelines (both for costs and outcomes) [28]. Also, it is often argued that the real interest rate of low-risk long-term government bonds is a good indicator for the social rate of time preference. In this case, the discount rate would oscillate at around 3 % [26,29,30]. Thus, in the base case, a discount rate of 3 % is recommended. Sensitivity analyses should apply 0, 5, 7 and 10 %. It is recommended that an identical discount rate is used both for the benefit and for the cost side. Reasons for deviations will be given in the preliminary report plan and experts may submit comments during the hearing procedure.

2.3.2 Potential for standardization

To improve comparability of health economic evaluations, standardization of costing methods is recommended, including the development of standard cost lists. Countries like Australia

[31], Canada [18,32] and the Netherlands [25,33] have presented standard cost lists that supplement guidelines for health economic evaluation. Standard cost lists present average valuations for commonly used services and resources.

In the Netherlands, for example, hospital costs (cost per inpatient day, differentiated between general and teaching hospitals), visits to general practitioners and specialists (costs per visit), valuation of medical staff time, costs of paid work (including friction period), costs of housework and travel costs are set and used throughout all health economic evaluations.

In Germany, the "Methods in Health Economic Evaluation" Working Group (AG Methoden der gesundheitsökonomischen Evaluation, AG MEG) of the German Society for Social Medicine and Prevention has calculated standard costs for the most relevant health services and resources [34].

3 Features of carrying out a cost estimation from the societal perspective

3.1 Identification of resource consumption

3.1.1 Classification of expenditure from societal perspective

All cost components are considered in the societal perspective, irrespective of who bears them and who benefits from the effects of an intervention. The cost estimation essentially includes:

- direct reimbursable medical costs of all social insurance providers
- direct non-reimbursable medical costs
- non-medical costs
- indirect costs

Generally, all costs that are incurred by all social insurance providers and others should be considered (see Table 1). Direct non-reimbursable medical costs primarily include the costs of health services that insurants have to pay for out of their own pocket. Costs incurred by patients and their family, for instance, are to be pooled under direct non-medical costs (e.g. travel costs). All other direct non-medical costs should be included here as well, such as the educational costs for sick or disabled students attending special schools (e.g. school for the visually impaired). In addition to direct costs, indirect costs in the form of productivity losses must also be considered. Patient time and family caregiver's time that represent lost working time, loss in net earnings by those concerned and transfer payments are not considered because these would lead to double counting if productivity losses were taken into account. Table 3 provides an overview of the common resource parameters in health economic evaluations from the societal perspective.

Cost category	Resource consumption
Direct medical costs (reimbursable and non-reimbursable)	Outpatient visits Procedures and diagnostics Drugs Medicinal substances Devices and medical assistive equipment Hospital stays Rehabilitation Services Other social insurance services
Direct non-medical costs	Services (including administration) Equipment and investments Travel costs Patient time (loss of leisure time) Informal care by family caregivers (loss of leisure time)
	Other direct non-medical costs (e.g. for visits to special training facilities)
Indirect costs	Reduced work productivity Incapacity for work Occupational disability Premature death

Table 3: Items of resource use from a societal perspective
Source: Adapted from Kobelt [3, p. 31]

3.1.2 Estimating indirect costs

When identifying indirect costs, opinions differ as to whether morbidity costs (due to incapacity for work or occupational disability) should be presented on the cost side or on the effect side of a cost-effectiveness ratio. The U.S. Panel on Cost-Effectiveness in Health and Medicine [35,36] advocates integrating productivity costs into a quality of life measure. This implies considering loss of productivity on the outcome side [6] under the assumption that patients take their loss of income due to illness into account when appraising their quality of life.

However, a large majority of the literature recommends putting productivity losses on the cost side [8,9,37-40]. It is argued that the usual quality-of-life approaches focus on pure health effects. None of the existing quality-of-life instruments ask patients to consider income effects due to lost working days [41]. Moreover, in the German context (with substantial sickness benefits), incapacity for work is associated with only partial income losses, which means that consideration of income losses due to incapacity for work would only have a minor impact on quality-of-life estimates. Thus, it is recommended that productivity losses due to incapacity for work are presented on the cost side.

There is agreement in the literature over not presenting productivity losses due to premature death (mortality costs) on the cost side when mortality is also considered on the benefit side, as otherwise double counting would occur as far as the individual is concerned. However, costs to the rest of the society (loss of taxes and social insurance contributions) must be considered on the cost side [37,40,41].

Unpaid work (e.g. housework) will be treated like paid work, i.e. mortality costs will be presented on the benefit side) and morbidity costs on the cost side, although valuation may be different (see Section 3.2.3).

In order to avoid double counting, mortality costs are always shown on the cost side for cases where the outcome considered does not relate to mortality or lifespan.

3.2 Resource valuation

3.2.1 Valuation of health care services

Cost estimation in health economic evaluations should reflect social opportunity costs. As mentioned above (Section 1.4.3), market prices in perfectly competitive markets reflect opportunity costs. However, most markets in the health care sector are imperfect as prices are regulated by public institutions (e.g. Doctors' Fee Scale within the Statutory Health Insurance Scheme [Einheitlicher Bewertungsmaßstab, EBM] for outpatient services and Diagnosis Related Groups [DRGs] for inpatient services), or are negotiated between associations of providers and health insurance funds (e.g. budgets for outpatient and inpatient care).

When using the micro-costing approach, quantification is based on the resource utilization (personnel, material, equipment, building, overheads, etc.) for health care services. As most resources are negotiated on competitive markets, it is recommended that resource prices are used for valuation.

Also, when cost estimation is focussing on medical procedures (e.g. examination, lab test, diagnostic imaging), it is recommended that market prices are used, if available, unless there are good reasons for adjusting to social opportunity costs [8,9]. Reasons for adjusting to opportunity costs are as follows:

- Market prices do not cover all costs if, for example, investment costs are financed separately. The DRGs in Germany do not include investment costs - these are financed by the federal states (so-called dual funding). Thus, an adjustment is justified, as, for example, in a mark-up for the estimated capital utilization (i.e. equipment and buildings).

- Excess profits are observed in a health market. A common adjustment is the determination of cost-to-charge ratios to remove excess profits [8,9].

- Different prices exist for identical services, depending on who is paying for these services (e.g. health insurance funds, statutory accident insurance, private health insurance). In Germany, for instance, physician fees for outpatient care differ between the SHI and private health insurance funds (based on the Medical Fee Schedule for care outside the Statutory Health Insurance Scheme [GOÄ], with higher reimbursements in private health insurance).

- Prices only form a charging unit independent of actual resource use (e.g. costs per inpatient day), and/or substantial cross-subsidization is observed.

When applying the macro-costing approach, there are often deviations in the societal perspective from the true social opportunity costs if the valuation is based on regulated "prices" and tariffs [4]. Similar adjustments to the social opportunity costs can then be justified as in micro-costing approaches. They are less imperative, though, since less precise cost estimates are accepted in macro-costing.

3.2.2 Valuation of drugs

The difference between market price and social opportunity costs is probably largest for patented drugs. Innovative drugs require substantial investment for research and development (R&D) which those who are responsible want refinanced as long as the drug is patented. During the period of patent protection the drug manufacturers may set monopoly prices. Thus, during the period of patent protection market prices will clearly be above opportunity costs.

Estimating opportunity costs for innovative drugs is difficult due to enormous information requirements. First, it should be decided whether long-term or short-term opportunity costs should be referred to [6,42]. Health economic evaluations commonly support decision making on investment decisions, which means that long-term marginal costs will be favoured. However, in the literature on drug opportunity costs, both approaches are discussed [6,42].

In the short term, only costs of production and distribution of the drug will be considered. A substantial part of total costs to society will not be included in the short-term, i.e. R&D investment, which is a fixed cost (and thus a sunk cost). In long-term decisions, R&D investment is part of social opportunity costs. R&D costs should be allocated to the span of the drug's life expectancy. Allocation of R&D costs could be performed by applying, for example, a capital user cost approach.

Another problem from a societal perspective is which part of R&D investment should be borne by a specific country (or: how R&D costs should be allocated to different countries). Possible approaches might be: (1) the (expected) country's share on the global market of the specific drug, or (2) the country's willingness to pay for the specific drug. Recommendations for the valuation of drugs are as follows:

- A rough estimation of long-term opportunity costs (on the basis of "market shares") might be performed.
- For other drugs (other than the intervention and the technologies compared in the health economic evaluation), adjusted market prices will often be sufficient for the estimation of opportunity costs as (1) the impact on total and incremental costs might be lower and (2) for non-patented drugs, the difference between market price and opportunity cost might be small(er).
- In the case of considering R&D costs, they should be reported separately. In addition, an analysis without considering R&D costs should be conducted.

3.2.3 Valuation of time lost by patients and their families

Time expenditure incurred by patients and their families is considered in the societal perspective if relevant and if the data is available. Diseases, particularly chronic diseases, often take up a substantial amount of the patient's time. For example, time is spent on receiving a treatment (including travel and waiting time), exercising, participating in training classes, or undergoing rehabilitation. A similar amount of forfeit leisure time is also spent by family caregivers (i.e. opportunity costs arise). Only the loss of leisure time may be taken into account but not the time lost through not working (or housework) because the latter is included under indirect costs (productivity losses).

In the literature it is recommended that loss in patients' leisure time should be entered on the benefit side, given that quality of life is taken into account in health economic evaluations [4,25,36,37]. It is expected that patients take the effect on their leisure time into account when estimating their quality of life. If possible, patients should be instructed to evaluate losses in leisure time under quality of life. However, as it is not certain that losses in leisure time are actually entered in the quality of life estimates (this applies especially when a representative random population sample evaluates the health conditions), losses in leisure time should be presented on the cost side in sensitivity analyses. Providing there are no data on quality of life for the health economic evaluations, leisure costs should be included on the cost side. As quality of life of family caregivers is not usually taken into account in the health economic evaluation, their loss in leisure time should be measured on the cost side.

An individual can divide their available time either between paid employment or leisure time. Opportunity costs of leisure time are accordingly net wages.

However, it is acknowledged that the effects on the leisure time of patients and their families are not taken into account in most empirical studies.

3.2.4 Assessment of indirect costs

As illustrated above (Section 3.1.2), lost time at paid and unpaid work (due to an incapacity for work) should be presented on the cost side. For the valuation of productivity losses, there are two fundamental methods, the human capital approach and the friction cost approach. The human capital approach suggests that health care interventions are a kind of investment in an individual's human capital (similar to education). According to the human capital approach, valuation of productivity losses is based on labour costs. All future productivity losses (up to retirement age) are considered in the human capital approach.

The friction cost approach assumes that for long-term incapacity for work, costs of productivity losses are limited to a so called friction period, i.e. until a patient is replaced by another employee and the former production level is restored. Costs according to the friction cost approach encompass productivity losses in the friction period and transaction costs (searching for and training the new employee). With short-term incapacity for work (within the friction period), part of the workload might be performed by colleagues of a patient or made up for by the patient upon their return to work. Thus, short-term productivity losses are less according to the friction cost approach than the human capital approach. Empirical studies in the Netherlands found that short-term costs are about 80 % of labour costs [43].

There is an ongoing debate in the literature whether the human capital approach or the friction cost approach is better at depicting productivity costs [43-46]. As mentioned above, the human capital approach is based on some unrealistic assumptions (particularly full employment in the labour market). The human capital approach shows potential rather than real productivity losses. In contrast, the friction cost approach focuses on real productivity losses. Nevertheless, the friction cost approach has been criticized, too. The assumption of zero opportunity costs of labour after the friction period in particular has implications for the calculation of direct medical costs. An advantage of the human capital approach from the societal perspective is that it can be transferred to housework (see below), while the friction cost approach is limited to paid work. In conclusion, it might be argued that the human capital approach is overestimating and the friction cost approach is underestimating opportunity costs. Thus, sensitivity analyses are recommended using the human capital approach as the base case.

In the health economic evaluation, valuation of indirect costs can be based on individual labour costs, i.e. gross wage rates plus wage supplements (in Germany, employer contributions to social insurance) or, alternatively, average labour costs. The calculation of the average labour costs per working day is based on the weighted average labour costs of full-time and part-time employed persons in Germany. The friction costs are assumed to be 80 % of wage costs (similar to the Netherlands). The friction period was derived from a company

survey on the filling of vacant positions [47]. In the literature, age-adjusted and sex-adjusted wage rates are also suggested. Therefore, average labour costs should be used for the base case.

3.2.5 Potential for standardization

From a societal perspective, it is possible to calculate standard costs in resource valuation particularly for inpatient costs and outpatient consultations.

- Inpatient costs include running costs (financed by SHI or private health insurance) and capital user costs (financed by the federal states). Capital user costs are modelled based on investment costs for new hospitals, assumptions about life span and utilization rates of equipment/buildings as well as assumptions about the appropriate interest rate.

- Costs per outpatient consultation are a weighted average of SHI and private insurance costs (with higher reimbursement in private health insurance). The calculation is based on the assumption that, on average, a physician earns a fair income (compared to other professions). The literature assumes that a weighted average price of inpatient and outpatient prices might be a good predictor for opportunity costs of pharmaceuticals [34]. As no information on inpatient prices and turnover is available, an adjusted outpatient price is recommended. This could be, for example, a pharmacy price net of discounts and rebates to health insurance funds. Rebates are now substantial in the German health care system as rebate contracts between pharmaceutical companies and health insurance funds are promoted in the legislation. An alternative might be to calculate the average price of the three lowest priced drugs in a drug class.

4 Features of carrying out a cost estimation from the perspective of SHI scheme insurants

4.1 Identification of resource consumption

According to the German Social Code Book V, the perspective of SHI insurants must be regularly included in the health economic evaluation (§ 35b (1) SGBV). According to this perspective, the services covered by the SHI and the costs that SHI insurants have to pay themselves (out-of-pocket expenses) are reproduced. The cost estimate includes the following:

- direct reimbursable medical costs
- direct medical and non-medical costs that have to be borne by patients and their families (non-reimbursable costs)

Direct reimbursable medical costs are all expenses for health services that are financed by the SHI. Direct non-reimbursable medical costs particularly include the costs for health services that insurants have to pay for out of pocket. This splitting between reimbursable and non-reimbursable costs is explained above in Section 1.3.3. The basic principles laid out in Section 2.1 apply in identifying the resource consumption of direct medical costs.

Under direct non-medical costs, travel expenses are particularly taken into account. Transfer payments (e.g. sick pay) and contributions to other social insurance benefits that are paid by the SHI in the event of illness are not considered in this perspective, as they do not primarily affect SHI insurants. The reason for this is that the finance flows are cancelled out through the solidarity-based financing of transfer payments and contributions. Loss of SHI contributions through illness is also not included for this reason.

Table 4**Fehler! Verweisquelle konnte nicht gefunden werden.** provides an overview of the most important resource parameters from the perspective of the SHI insurants.

Cost category	Resource consumption
Direct medical costs (both reimbursable and non-reimbursable)	Outpatient visits (including consultation fee) Procedures and diagnostics Drugs (including co-payments) Medicinal substances (including co-payments) Devices and medical assistive equipment (including co-payments) Hospital stays (including co-payments) Rehabilitation (including co-payments) Services (including co-payments)
Direct non-medical costs	Travel costs Overheads (e.g. administration)

Table 4: Items of resource use in the health economic evaluation from the perspective of the SHI insurants

4.2 Measuring resource consumption

The appropriate level of precision in measuring services and resources is influenced, for instance, by the tariff system and particularly by the service units, which are stipulated in a fixed pricing system. As tariffs in the inpatient sector in Germany are based on a DRG system (with the exclusion of psychiatry), diagnoses should be identified and quantified accordingly using the DRG system, whereas a detailed recording of the medical services would not be appropriate. This restriction particularly pertains to the inpatient reimbursable costs, while it might make much more sense to apply a micro-costing approach in order to quantify the co-payments (see also Section 2.2).

4.3 Prices and expenditure in resource valuation

In general, administered and negotiated prices on health care markets determine expenditure, representing opportunity costs to the SHI insurants. Thus, in contrast to cost estimation from the societal perspective, normally there will be no adjustments of (administered and negotiated) market prices.

Nevertheless, some sector-specific budgets might impact on opportunity costs to SHI insurants. For example, in the hospital sector, a target hospital budget is negotiated between the hospital and the health insurance funds. Hospital care is remunerated according to DRGs, but once the target budget is reached, remuneration and thus opportunity costs from the health insurance funds drop to 35% of the usual remuneration. Alternatively, an increase in hospital

care services for some patients (e.g. patients from an evaluation study) might induce a decrease in hospital care services for other patients (e.g. through early discharge) because the hospital might want to avoid exceeding its target budget.

Early discharge of other patients may induce opportunity costs to SHI insurants. To be precise, opportunity costs accrue when an additional, medically-justified expenditure occurs in other sectors, or through later readmissions due to complications. Thus, there might even be zero opportunity costs (if early discharge does not induce additional expenditure). In sensitivity analyses, the impact of lower opportunity costs should be calculated. In other health care sectors there are similar impacts of sector-specific budgets on opportunity costs (for more details, see Krauth et al. [34]).

As mentioned above (see Section 4.2), the tariff system defines the maximum grade of precision in expenditure calculation (i.e. micro-costing versus macro-costing approach is applied). For example, in hospital care, prices are based on a DRG system. Thus, DRGs are the most precise expenditure valuation (for hospital care) in health economic evaluation studies from the SHI insurants' perspective. Less precise valuations (e.g. expenses per inpatient day) can be derived (see Section 2.3.2). In the primary care sector, there is a detailed price system (Doctors' Fee Scale by reimbursement through the SHI), specifying prices for a broad range of medical procedures (e.g. examination, lab test, diagnostic imaging, etc.). Again, it is possible to derive less precise valuations (e.g. expenditure per consultation).

Non-reimbursable costs, in other words out-of-pocket costs borne by the patient, are partially regulated, so that relevant standardization in resource valuation can be used (e.g. co-payments for drugs). Appropriate market prices should be set for out-of-pocket expenditure that is not regulated by the state (see Section 3.2.1).

4.4 Allocation to the social security perspective and the SHI perspective

In contrast to the SHI insurants' perspective, in the social security perspective the overall social security expenditure is taken into account but not the co-payments that insured individuals have to make. This includes all sickness-related expenditure of the SHI, statutory care insurance (e.g. for long-term care), statutory pension insurance (e.g. rehabilitation services for employable persons), statutory accident insurance (accidents at work and occupational diseases), and unemployment insurance. Depending on the commission of the health economic evaluation, it may also be necessary to include only the perspective of individual social insurance providers in addition to the SHI insurants' perspective. The sickness-related costs can fluctuate greatly depending on the perspective of the social insurance provider (e.g. from health insurance to pension insurance – particularly in rehabilitation projects or in valuating care given by the family, between which the SHI and the long-term care insurance would differentiate).

The pure SHI perspective not only differs from the SHI insurants' perspective in that the patient's co-payments are not being taken into account; for example, transfer payments (e.g.

sick pay) also have to be valuated in the SHI perspective, as well as the share of contribution payments for pension insurance, long-term care insurance and unemployment insurance, which the SHI has to bear in the event of sickness after six weeks' incapacity for work. In contrast to the SHI insurants' perspective, the loss of contributions (e.g. while receiving sick pay) must be taken into account from the pure SHI perspective.

However, it needs to be pointed out here that, according to the interpretation of § 35 SGB V, the pure SHI perspective cannot be included in IQWiG's health economic evaluation. In fact, depending on the commission, it is possible to carry out the health economic evaluation from the perspective of an individual or several social insurance providers (pension insurance, long-term care insurance, unemployment insurance) or from the societal perspective, in addition to the SHI insurants' perspective.

5 Data sources

5.1 Data sources for health economic evaluations

Health economic evaluations combine data for the cost side from a broad variety of sources that are listed according to category in Table 5**Fehler! Verweisquelle konnte nicht gefunden werden.**.

Data source	Examples
Studies	Clinical trials
	Observational studies
	Reviews
Administrative data	Health insurance funds
	Private health insurance
	Statutory pension insurance
	Statutory long-term care insurance
	National Association of SHI Physicians
	German Hospital Federation
	Hospitals
Other data	Official statistics (e.g. Federal Statistical Office InEK [Institute for the hospital remuneration system])
	Registries (e.g. myocardial infarction, cancer)
	Surveys
	Guidelines
	Questionnaires
	Expert opinion (for identifying relevant resources)

Table 5: Data sources for the cost side

5.2 Transferability of cost data

In general, health economic evaluations will include study results from foreign countries. As is documented by the increasing amount of literature on transferability of cost data (e.g. [48-53]), the transfer of cost data from the studied country to the target country should be performed with care.

Welte et al. [54] developed a framework to examine the transferability of cost data from foreign studies. This framework describes (1) factors influencing transferability of cost data, (2) key determinants influenced, (3) efforts to check correspondence between studied and target country, and (4) adjustments to improve transferability to the context of the target country.

A selection of factors that might affect the transferability of study results are [48,52,54]:

- population characteristics (examples)
    - incidence/prevalence of diseases
    - case-mix
    - life expectancy
- health care system characteristics (examples)
    - absolute and relative prices
    - clinical practice variation
- methodological characteristics (examples)
    - perspective
    - discount rate
    - productivity cost approach

There are criteria (general and specific) that will preclude transferability of cost data:

- The intervention, evaluated in foreign countries, or the comparators are not relevant to the target country (e.g. a comparator drug is not licensed in the target country).
- The study quality does not meet the methodological standards of the target country.
- Each transferability factor can become a (specific) knock-out criterion.

Modelling adjustments are absolutely necessary when there are large differences between study and target country in (1) incidence/prevalence, (2) practice variation, or (3) relative prices. However, every other transferability factor might lead to adjustments as well. Adjustments may concern the structure of the decision model (to adapt to different health care processes) or the resource utilization. Adjustments of valuation (unit prices) should always be carried out. Furthermore, adjustments should be made for inflation and different currencies. For currency conversion, purchasing power parities are recommended. For more details see Welte et al. [54].

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