German Recommendations on Health Economic Evaluation: Third and Updated Version of the Hanover Consensus

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Prolog

Financial restrictions and a stronger focus on outcomes assessment require rational decisions regarding the allocation of resources in the health-care system. Such decisions are based on medical, ethical, and economic considerations. Management of the health-care system requires both a medical and an economic orientation at the overall societal level and regarding the selection of appropriate health-care services in hospitals and ambulatory practices. The practical application of health economic methods can be an important tool assuring more transparency and in validating necessary decisions.

The methods made available by health economic research represent a rational approach for a structured resource allocation in the health-care system and facilitate the process of a relative assessment of various treatment methods with each other. Although the focus of such studies frequently rests on pharmaceuticals, health economic evaluation methods are suitable for all medical services, procedures, and health-care programs. But, what is assessed from which perspective, Novartis Pharma GmbH, Nuremberg; Sonja Merkesdal, Medical University Hanover, Hanover; Rolf Mueller, AOK Berlin—Die Gesundheitskasse, Berlin; Udo Mueller, Deutsches Krankenhausinstitut e.V., Duesseldorf; Axel Munte, Kassenärztliche Vereinigung Bayern, Munich; Guenter Neubauer, Universitaet der Bundeswehr Munich, Munich; Peter Obenderer, Universitaet Bayreuth, Bayreuth; Ulrike Osowski, Merck Pharma GmbH, Darmstadt; Juergen Peter, AOK—Die Gesundheitskasse für Niedersachsen, Hanover; Bernd Raffeltueschen, Forschungszentrum Generationenvertrag, Freiburg; Karin Rauner, Serono GmbH, Unterschleissheim; Ansgar Resch, Pfizer Deutschland GmbH, Karlsruhe; Walter Ried, University Greifswald, Greifswald; Alric Ruether, DIMDI, DAHTA@DIMDI, Cologne; Claus Runge, Wyeth Pharma GmbH, Muenster; Reinhard Rychlik, Institut für Empirische Gesundheitsökonomie, Burscheid; Wolfgang Schmeinck, BKK Bundesversicherung, Essen; Willi Schnorpfel, Novo Nordisk Pharma GmbH, Mainz; Gerhard Schulte, BKK Landesversicherung Bayern, Munich; Hanns J. Schultes, Novartis Pharma GmbH, Nuremberg; Hans-Nikolaus Schulze-Solce, Lilly Deutschland GmbH, Bad Homburg; Peter Scriba, University Munich, Munich; Hans-Konrad Sellmann, University Tuebingen, Tuebingen; Uwe Siebert, UMIT, Hall i. T., Austria; Till C. Sprio, Kassenärztliche Vereinigung Bremen, Bremen; Volker Ulrich, University Bayreuth, Bayreuth; Johannes Voekting, Barmer Ersatzkasse, Wuppertal; Ingo Werner, BKK Landesverband Niedersachsen-Bremen, Hannover; Eberhard Wille, University Mannheim, Mannheim; Stefan N. Willich, Charité, Berlin; Cornelia Yzer, Verband Forschender Arzneimittelhersteller e. V., Berlin.

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the selection of instruments and under which objectives depends on the decision-maker for whom the evaluation is conducted as a decision-making aid and the normative requirements stipulated by that particular decision-maker. It is not the objective of health economic studies to make decisions based on the results of the specific study situation but to make value judgments and assessment criteria of the decision-maker transparent and to make his or her decision and the underlying decision process easier.

All benefit parameters that are relevant for the study situation in question should be incorporated in the assessment. It may be that data from various sources must be taken into account, which can be accomplished with the help of models. Possible essential data sources include medical meta-analyses, randomized clinical studies, as well as epidemiological observational data on the disease or long-term impacts of the disease. Additional relevant sources are cohort studies, data from health-care services research, data on current therapy standards, and possibly also expert opinions wherever other evidence is not available.

Furthermore, the various dimensions of a treatment benefit should be addressed by collecting and assessing data on the efficacy, tolerability, quality of life, patient satisfaction, benefit of compliance, or ability to work. The goal of the health economic analysis is the assessment of benefits of a new treatment compared to an alternative treatment (effectiveness); for decisions regarding coverage packages of health insurance funds, the comparison to standard treatment in everyday clinical practice is frequently chosen. The study form to be chosen depends on the benefits of interest and the way those are supposed to be linked to costs (e.g., cost comparison analysis, cost-effectiveness study, cost-utility analysis). A cost–benefit analysis can be appropriate, if it is methodologically ensured that all benefit dimensions are covered in the analysis.

The “Hanover Consensus” provides a health economic “construction kit” that aims at making the development process of health economic studies easier and to standardize studies in terms of applied methods. It was first published in 1996 and revised for the first time in 1999. The endorsing individuals from academia and health-care practice support it overall and in person. In doing so, they do not express the potential position of the institution with which they are professionally associated.

This guideline for health economic evaluation is supposed to represent the framework for conducting health economic evaluation studies in Germany. Deviations from this guideline seem possible but should be justified. Hence, the “Hanover Consensus” is meant to provide standards on the one hand and to promote methodological progress and scientific innovation in health economics on the other. For this purpose, scientific freedom is indispensable, which is explicitly acknowledged by the consensus group. With this in mind, rules or policies in this guideline are only stipulated for those items that are theoretically and practically considered indispensable minimum requirements for evaluations which are already reflected by and an integral part of high-quality studies today. In the future, this health economic consensus group will be an open task force coming from academia and practice and will continue (if needed) to regularly develop recommendations on health economic evaluation research.

Study Design
A health economic study should be conceptualized and structured in concordance with scientific standards. This includes the explicit statement of the objective, the derivation of the hypotheses, the description of the methodology, a justification of the alternatives to be evaluated, as well as the definition of the perspective and the target population. With regard to the last variable, it must be stated in which patient (or study) groups the data in question were collected and to which patient groups the outcomes are supposed to apply. A study protocol on medical, economic, and statistical questions and procedures must be prepared before commencing a study. In each case regarding health-care supply, the most realistic study design should be chosen and implemented.

In contrast to clinical studies that are typically designed with regard to a “Proof of Concept” concerning, e.g., the clinical mode of action of a specific substance, economic evaluations are based on modeled assumptions or ideas. These allow the illustration of questions related to fairness, distribution, or allocation issues in the provision of health-care services that are of particular interest to decision-makers. To address these issues and to enable the combination of various different data sets, the selection of an appropriate study form frequently requires health economic modeling. Through that approach, results and statements for longer time horizons and also the impact of the variation of parameters on the results can be enabled and tested.

Distributive and ethical problems and issues can be incorporated in the study if this is required by the primary study objective and justified by available databases and relevant literature. In any case, the distribution premises must be indicated explicitly. The existing health-care provision, organization, and allocation are also based on value judgments, so that any status quo is not neutral in its value judgments.

Perspective
The perspective describes the point of view from which costs and benefits are collected and assessed. Depend-
ing on the objective of the study, various perspectives can be meaningful in cost assessments (e.g., perspective of the overall social security system, the health-care system as part of the latter, the health insurance funds, hospitals, physicians, or patients). If possible, when considering individual components of the costs and benefits, it should be ensured that the perspective is synchronized in both outcome dimensions. Priority should be given to the societal perspective. Legitimate deviations from that must be justified in detail based on the decision-making situation in question. The choice of perspective per se must be justified and logically elaborated from the decision problem. If several perspectives are taken into account in one study, the assumptions and results must be separately indicated for each study perspective.

Study Forms

Health economic studies can be classified with regard to the type of variables that are assessed and according to their analytical approach. The choice of the type of analysis depends on the study subject as well as the purpose of the study, and must be justified accordingly. Complete health economic evaluation studies, especially cost-effectiveness and cost-utility studies, aim at comparing costs and consequences of various measures. Cost–benefit analyses are appropriate when the methodological issues regarding the transformation of intangible effects into monetary units are sufficiently addressed. Over the past few years, comprehensive research has been conducted in this area, allowing the use of these study forms if sufficient substantiation in the literature from a methodological and scientific point of view can be demonstrated.

The cost-of-illness analysis should be mentioned as an additional study form. Cost-of-illness studies are meant to provide information on the frequency of specific diseases, the types of relevant therapies, the frequency and costs of different therapies, and other general issues or facets of the illness in question. This study form has a special importance in the assessment of the economic relevance of a disease to society. As part of cost-of-illness analyses, descriptive cost-comparison analyses looking at defined disease subgroups can also be conducted.

When conducting the study, the relevant current state of the art guidelines (especially Good Clinical Practice (GCP) for randomized clinical studies, Good Epidemiological Practice, and the recommendations of the Cochrane Group) should be applied. For all study forms, the literature research itself, the assessment of the cited literature, the modeling algorithms and calculations, as well as the computer programs used should be documented thoroughly, and the underlying assumptions clearly justified.

If the available cost and efficacy or effectiveness data do not consist of sufficient external validity, because current health-care practice is insufficiently represented, health economic modeling via decision-analytical methods can be conducted. For this purpose, all data sources used and the structural and quantitative assumptions made must be disclosed, the model structure must be justified in detail, and its robustness must be thoroughly tested through sensitivity analyses. In addition, the software program to conduct the modeling must be indicated. If intermediate or surrogate outcome parameters are used to estimate effectiveness, their effect on patient-relevant outcome parameters such as mortality, morbidity, and the burden of treatment must be demonstrated based on scientific evidence. The modeling results should be verified in practical health-care services research studies (e.g., cohort studies, pragmatic clinical studies, registries) as soon as possible.

Selection of Alternatives

The objective of a health economic evaluation is the disease-specific comparison of a specific therapy with alternative courses of action. The comparison should be made in light of a complete description of relevant treatment pathways within the health-care system. The study may compare the approach in question with the most frequent, the most clinically effective, or the most efficient alternative or pathway. In doing so, the alternative of nontreatment may also be considered. The choice of reference alternative(s) must be justified.

Validity and Data Sources

Data sources for health economic evaluation studies include information on the medical efficacy or effectiveness of certain alternatives, as well as information on the economic consequences of each alternative. In addition, economical, medical, and epidemiological frameworks of health-care provision should be taken into account. All data sources used in a health economic evaluation must be described in detail, and their selection with regard to the study objective as well as the perspective must be justified and assessed in terms of their suitability and their internal and external validity. Clinical studies generally have high internal validity which may be accompanied by low external validity. In such a case, such studies should be supplemented by high-quality health economic studies with greater external validity.

The comparative quantification of the effectiveness of treatment alternatives requires studies that have a scientific design comparable to the designs in randomized, controlled studies. As a prerequisite for economic considerations in a specific case, clinical studies evaluating medical efficacy are indispensable. Nevertheless,
as mentioned before, clinical studies often cannot serve as the sole basis of information for a health economic assessment. A realistic estimate of the costs can be limited under study conditions, if the use of some health-care services only arises from the study plan. In addition, clinical studies mostly cover only a brief period of time, the indication is narrowed down, and populations in terms of inclusion and exclusion criteria (e.g., complications and age) are strongly selected. Furthermore, studies are mainly statistically powered to investigate the medical efficacy of a specific treatment and therefore the study sample is too small to be able to reflect rare events with serious economic consequences. Hence, in many cases, models, for which requirements are described in the “Study forms” section, can achieve better external validity. When expert opinions are included in such studies, the selection criteria of the panel and the process of forming consensus must be disclosed and described in detail.

Cost Determination

In principle, all relevant costs and outcome variables for the selected perspective must be taken into account. Reported direct costs should cover all resources used (capital and administration costs may also be included, depending on the chosen perspective) that are associated with the medical treatment. Direct medical costs are directly incurred by the treatment process itself (e.g., costs of pharmaceuticals). Direct nonmedical costs include all resources used as a consequence of the therapy or illness (e.g., transportation costs, costs in the educational system, or direct costs for household help required as a consequence of the illness). From a societal perspective, in particular partial areas of health care, e.g., informal or formal care for individuals in need of help, the burden to caregivers may be an area of interest in determining costs. If that burden can be transformed and valued in monetary terms (e.g., giving up one's job to care for an individual), it must be taken into account. If the valuation in monetary terms justifiably cannot be conducted, such use of resources should at least be listed quantitatively.

Generally, the use of resources must be reported separately from prices in quantitative units. Ideally, the valuation of direct and indirect usage of resources in monetary terms is made with the help of opportunity costs. With this approach, one can determine what benefit the used resources would have achieved in the next best alternative. As a result, resource consumption should be priced at market procurement prices. If this is not possible, administered prices (e.g., remuneration schemes from the statutory insurance) and average values also can be used.

A marginal analysis should be performed to quantify the costs and outcomes of an additionally produced unit. Averages should only be used, if marginal values are unavailable. In this case, the use of average prices must be pointed out explicitly.

When interpreting the costs, an overestimation of costs due to components not fully attributable to the disease must be avoided. For a study taking the societal perspective, existing inefficiencies in the system and their cost-effects also should be listed and discussed separately. If the intervention to be analyzed has an impact on comorbidities associated with the indication, these should be included in the analysis, if this is relevant from the selected study perspective. Any resulting data must also be reported separately and discussed with regard to effects.

Indirect costs comprise all other costs caused indirectly through the treatment or the illness, including sick leave days at work. Apart from losses based on absence from work, the reduction in the ability to perform (at the respective work) can be reported separately. As for its relative importance, the latter has a more informative character, because resulting welfare losses are methodologically difficult to collect. Nonetheless, these specific productivity losses may be more relevant under certain study perspectives, but this must be separately justified and discussed.

As no full employment exists in industrialized countries, open positions can typically be refilled within a relatively short period of time. One way to account for this fact is to only assess the time frame up until a worker has been replaced (friction period) as a loss in productivity (e.g., early retirement due to the illness). Short-term productivity losses must be assessed more cautiously. Typically relevant job duties are at least partially performed by other employees during the individual’s illness or by the individuals themselves after their return to work.

The value of the productivity losses is the work time lost through illness multiplied by the market value of this work time, e.g., represented by the wage costs per time unit from the perspective of the employer (i.e., wages plus premiums to social insurance schemes payable by the employer). The chosen approach of calculation must be presented and justified in detail for all used reference groups (e.g., if there are differences according to age or sex). Furthermore, as a reference, the results should be recalculated taking the value of a lost work day using the terms “overall employees” compensation in Germany per year (including social insurance premiums) divided by “number of employees times 365.” The nomenclature used in this formula corresponds to the wording from the official statistics of the Federal Statistical Office. By using the official figures from 2006, one obtains a rounded value of €90 per lost day of work. Naturally, this example changes over the course of time, which is why this amount has to be adjusted continuously.
Deviation from that formula should be discussed and justified. With this approach, sick leave days falling on Sundays and holidays must also be considered. The average productivity loss resulting from the above-described calculations is also used for self-employed individuals. Depending on the perspective, transfer payments may also be taken into account, but attention must be paid to the risk of double counting.

Collection of Outcome Parameters

The suitability of outcome parameters depends on both the disease and the study question of the economic evaluation. Within a study setting, mortality- and morbidity-related parameters as well as clinical, nonintermediate states, quality of life-related outcomes, and other parameters can be used. The selection of outcome parameters must be justified.

The subsequent assessment of study results is made easier by choosing outcome parameters that have already been validated in the literature and are accepted for that indication. Guidelines and recommendations of the relevant medical specialists’ group(s) should be considered. If no such instruments or outcome parameters are commonly accepted or available within that specific specialists’ group, the choice must also be justified in detail.

When applying cost-effectiveness and cost-utility analyses, the selection of outcome parameters is of key importance. If utility values (e.g., quality-adjusted life-years [QALYs]) are included in a study, these should be preferably determined through direct generation of individual values via standard gamble, the time-trade-off method, or with validated, preference-based, generic instruments (e.g., EQ-5D or SF-6D). The validation and preferences of these questionnaires should be based on a representative population sample from Germany. In specific study situations the application of a visual analog scale (VAS) can also be appropriate, if the validity of the information can be justified. In well-substantiated exceptions, it is acceptable to deviate from population-based preference values.

Time Horizon

The selection of the time horizon depends on the study subject and can range from just a few weeks to a lifelong time period for chronic diseases or preventive services. In any case, the entire time span, during which an impact of a study alternative on resource usage, effectiveness, outcomes, utilities, or quality of life can be expected or has been substantiated by previous research data, must be analyzed. Models are often required because of the fact that, at the time a health economic assessment is conducted, no comprehensive data have been generated in most cases to cover relevant time horizons (e.g., data on effects of a therapy after the conclusion of clinical trials). Based on the study subject, several relevant time points should be set for the cost-effectiveness calculations (if this study form is selected).

Discounting

If costs and/or health effects (outcomes) are accrued for more than 1 year, the calculation of present values is necessary to ensure comparability of payment flows and the associated benefit. An annual reference discounting rate must be set at 5%, and the robustness of the outcomes should be checked with higher and lower discounting rates (0%, 3%, 10%) as part of the sensitivity analyses. The discounting rate for costs and health effects (e.g., QALYs) should be chosen identically. Deviations must be specially justified and checked in sensitivity analyses.

Sensitivity Analyses

All outcomes must be checked for their reliability (robustness) and their dependence on individual input parameters used (costs and benefits).

In all cases, the influence of individual parameters must be analyzed via a univariate approach. For this purpose, the individual input parameters are varied within a range, which may be based on realistic considerations or a schematic variation (e.g., variation by percentages).

If possible, the robustness should be analyzed as part of a probabilistic approach, with each input parameter being included according to its specific distribution, which should be based on empirically determined values including their dispersion. A distribution can be assigned to missing data, but that has to be justified in detail. Alternatively, a different multivariate approach can be chosen that varies multiple parameters simultaneously during the analysis.

Independent of the selected method for the sensitivity analysis, the variation range must be discussed and justified in each case. Furthermore, it is recommended to develop and discuss hypothetical worst-case and best-guess scenarios. The results of the sensitivity analyses must be critically discussed and assessed in terms of their stability and ethical implications.

Presentation and Discussion of Outcomes

All outcomes must be reported with the relevant statistical measures of dispersion. In addition, the outcomes must be discussed with regard to their generalizability outside the chosen study setting and set in reference to previously known and published data. Furthermore, all previously defined research questions should be answered and addressed with the help of the study results. Discussion of the outcomes must always
be made in light of the German health-care context as well as the chosen perspective. As part of the concluding discussion, the key limitations and uncertainties of the outcomes and methods must be indicated and critically addressed. Moreover, relevant key conclusions and recommendations for decision-makers should be stated.

Publication of Outcomes

Health economic studies must be transparent. As a result, their quality also depends on the extent of their publicity and availability. Study results should be published in journals that have a peer review policy prior to publication. Choosing not only health economic journals but also scientific journals of the respective medical field is appropriate. For methodologically complex studies, it is advantageous to generate a detailed methodological documentation in addition to the publication that can be made available on request. Significant outcomes should be presented in aggregated and disaggregated form. The authors must ensure (e.g., with technical appendices) that the outcomes of complex studies (e.g., comprehensive modeling studies) can be followed by an expert third party. The results of the study must be compared to the results of other studies with a similar study question. Methodological differences and different study conditions should be pointed out and addressed in detail, because different study conditions and populations may contribute to different outcomes. If possible, the potential relevance and consequences of the study results should also be stated for decision-makers.

In accordance with existing policies for clinical trials, the study should be published independent of the results. Conflicts of interest must be stated in the publication.

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