General Methods[a]

Version 6.1 of 24 January 2022

[a] This translation is based on the German document *Allgemeine Methoden* (Version 6.1) of 24 January 2022. Please note: The translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Tel.: +49 221 35685-0
Fax: +49 221 35685-1
E-Mail: methoden@iqwig.de
Internet: www.iqwig.de

Preamble

The Institute for Quality and Efficiency in Health Care (IQWiG[b]) is an establishment of the Foundation for Quality and Efficiency in Health Care. IQWiG is a professionally independent scientific institute. Information on the structure and organization of the Foundation and the Institute is available on the website www.iqwig.de.

The *General Methods* explain the legal and scientific basis of the Institute. Its tasks are described in this document, as are the scientific tools applied in the preparation of its products. Hence, the Institute's methods paper provides an important contribution towards transparency in the Institute's mode of operation.

The *General Methods* are primarily directed at researchers. In order to make the information on the Institute's mode of operation accessible to as many interested persons as possible, the authors have aimed to produce a comprehensible document. However, as with any scientific text, a certain level of prior knowledge on the topic is assumed.

The *General Methods* aim to describe the Institute's procedures in a general manner. What specific individual steps the Institute undertakes in the assessment of specific medical interventions depend, among other things, on the research question posed and the available scientific evidence. The *General Methods* should therefore be regarded as a kind of framework. How the assessment process is designed in individual cases is presented in detail for each specific project.

The Institute's methods are usually reviewed annually with regard to any necessary revisions, unless errors in the document or relevant developments necessitate prior updating. Project-specific methods are defined on the basis of the methods version valid at that time. If changes are made to the general methodological procedures during the course of a project, then it will be assessed whether project-specific procedures need to be modified accordingly. In order to continuously further develop and improve its mode of operation, the Institute presents its *General Methods* for public discussion. This applies to the currently valid version, as well as to drafts of future versions.

[b] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

What is new?

In comparison with Version 6.0 of the Institute's *General Methods* of 5 November 2020, in Version 6.1, minor errors were corrected and editorial changes made. In addition, a literature update was conducted. The following changes to content and structure were made:

- amendments in Sections 1.1 and 1.3 on evidence searches as the basis for the development and updating of guidelines
- deletion of Section 1.5 on evidence-based decision-making in health care
- amendments in Sections 2.1.11 and 2.2.1 on evidence searches for guidelines and the new product "evidence report"
- waiver of disclosure of relationships of affected persons in Sections 2.2.1 and 7.14
- amendments to Section 3.1.4 regarding the qualitative summary of study results using the concept of conclusive effects
- amendments to Section 3.3.3 on determining the extent of added benefit in the case of continuous data
- renaming of Chapter 5 in "Analyses of health care"
- amendment of Section 5.1 on evidence searches for guidelines
- modification of Section 5.2.1 on the background of guideline synopses
- inclusion of the reporting guideline PRISMA-S in Chapter 8
- amendments in Section 9.3.7(A) with regard to evaluating when a common effect estimate is meaningful

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Definition
AGREE	Appraisal of Guidelines Research and Evaluation in Europe
AHP	analytic hierarchy process
AMNOG	Arzneimittelmarktneuordnungsgesetz (Act on the Reform of the Market for Medicinal Products)
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ANV	AM-NutzenV, Arzneimittel-Nutzenbewertungsverordnung (Regulation for Early Benefit Assessment of New Pharmaceuticals)
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies)
BIA	budget impact analysis
CA	conjoint analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CERQual	Confidence in the Evidence from Reviews of Qualitative Research
CONSORT	Consolidated Standards of Reporting Trials
DMP	disease management programme
DMP-A-RL	DMP-Anforderungen-Richtlinie (DMP Requirements Directive)
DRG	diagnosis-related group
EBM	evidence-based medicine
EMA	European Medicines Agency
EU-CTR	EU Clinical Trials Register
EUnetHTA	European network for Health Technology Assessment
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GoR	grade of recommendation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HEE	health economic evaluation
HTA	health technology assessment
ICTRP	International Clinical Trials Registry Platform Search Portal
IPD	individual patient data
IQR	interquartile range
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention to treat

Abbreviation	Definition
LoE	level of evidence
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
NHB	net health benefit
NICE	National Institute for Health and Care Excellence
NUB	Neue Untersuchungs- und Behandlungsmethoden (new examination and treatment methods)
NVL	Nationale VersorgungsLeitlinie (National Health Care Guideline)
OECD	Organization for Economic Co-operation and Development
PICO	population, intervention, comparison, outcome
PRESS	Peer Review of Electronic Search Strategies
PRISMA(-S)	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (-for Searching)
PRO	patient-reported outcome
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RCT	randomized controlled trial
ROBIS	Risk of Bias in Systematic Reviews
SGB V	Sozialgesetzbuch – Fünftes Buch – Gesetzliche Krankenversicherung (Social Code Book – Book V – Statutory Health Insurance)
SHI	statutory health insurance
SMD	standardized mean difference
STE	surrogate threshold effect
WHO	World Health Organization

A chief cause of poverty in science is mostly imaginary wealth. The aim of science is not to open a door to infinite wisdom but to set a limit to infinite error.

Bertolt Brecht. Life of Galileo. Frankfurt: Suhrkamp. World premiere, first version, Zurich theatre, 1943.

1 The Institute for Quality and Efficiency in Health Care

1.1 Legal responsibilities

The Institute was founded within the framework of the German Health Care Reform of 2004 [169] as an establishment of the Foundation for Quality and Efficiency in Health Care. The legal basis and responsibilities of the Institute have been anchored in Social Code Book Fifth Book – Statutory Health Insurance (SGB[1] V) [4] and adapted and extended several times in the course of further health care reforms. More information on the Institute's structure and organization is available on the website www.iqwig.de.

The Institute addresses issues of fundamental relevance for the quality and efficiency of statutory health insurance (SHI) services. Its specific responsibilities are outlined in detail in §139a SGB V:

- search for, assessment and presentation of current scientific evidence on diagnostic and therapeutic procedures for selected diseases
- preparation of scientific reports, expert opinions, and comments on quality and efficiency issues of SHI services, taking age, gender, and personal circumstances into account
- search for evidence on the current state of medical knowledge as a basis for the development or further development of clinical practice guidelines
- appraisal of evidence-based clinical practice guidelines on the most relevant diseases from an epidemiological point of view
- issue of recommendations on disease management programmes (DMPs)
- assessment of the benefit and cost of drugs
- provision of easily understandable information for all patients and consumers on the quality and efficiency of health care services, as well as on the diagnosis and treatment of diseases of substantial epidemiological relevance
- involvement in international projects on the collaboration and further development in the field of evidence-based medicine (EBM)

[1] Sozialgesetzbuch: regulates the statutory health care services.

The modalities of the commissioning and performance of tasks are specified in §139b SGB V. According to this law, only the Federal Joint Committee (G-BA[2]) or the Federal Ministry of Health[3] may commission the Institute. In the case of commissioning by the Ministry, the Institute can reject a commission as unfounded, unless the Ministry funds the project. According to §139b (6) SGB V, this option does not apply to the commissioning of evidence searches for the development or updating of clinical practice guidelines.

The Institute must ensure that external experts are involved in the work on commissions. In order to ensure the Institute's scientific independence, these experts are required to disclose all connections to associations and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received (see Section 2.2.3).

The Institute submits the results of the work on commissions awarded by the G-BA to this body in the form of recommendations. According to the law, the G-BA must consider these recommendations in its decision-making processes.

The G-BA may withdraw, suspend or change commissions to the Institute. The procedure is described in Chapter 1, §16b (3) of the Rules of Procedure of the G-BA [271]. Accordingly, these decisions are taken in consultation with the Institute.

The Institute is largely funded by contributions of SHI members. For this purpose, a levy is determined by the G-BA in accordance with §139c SGB V. This levy is paid by all German medical practices and hospitals treating SHI-insured patients.

Within the framework of the Act on the Reform of the Market for Medicinal Products (AMNOG[4]), at the beginning of 2011, the Institute's responsibilities were extended to the assessment of the benefit of drugs with new active ingredients shortly after market entry [171]. For this purpose, manufacturers must submit dossiers summarizing the results of studies. The G-BA is responsible for this "early benefit assessment"; however, it may commission the Institute or third parties to examine and assess the dossiers.

The new regulations in §35a SGB V are the basis for these assessments. They are supplemented by a legal decree of the Federal Ministry of Health [106], which has also been effective since the beginning of 2011, and the G-BA's Code of Procedure [271].

[2] Gemeinsamer Bundesausschuss: The G-BA is the decision-making body of the self-government of the German health care system. More information on the Committee's responsibilities is provided at www.english.g-ba.de.

[3] Bundesministerium für Gesundheit, BMG

[4] Arzneimittelmarktneuordnungsgesetz

In connection with a benefit assessment, the G-BA can also commission the Institute to conduct a health economic evaluation (HEE). The framework of these HEEs is specified in §35b SGB V and §139a SGB V.

In this context, cost-effectiveness ratios of medical technologies are compared with the aim of providing information on the basis of which the appropriateness and reasonableness of cost coverage by the community of SHI insurants can be considered.

The HEE itself is based on a comparison with other drug or non-drug interventions. In particular, the following criteria to determine the benefit for patients are named in the law: increase in life expectancy, improvement in health status and quality of life, and reduction in disease duration and adverse effects. The definition of a "patient-relevant benefit" valid for the Institute is inferred from the above specifications in the law (see Section 3.1).

Within the framework of the Structure of Health Care Act, in 2012 changes were made to §137c SGB V and §137e SGB V was added. This gives the G-BA the option to initiate clinical studies on new examination and treatment methods (testing), provided that the benefit of a method has not yet been sufficiently proven but its potential as a necessary treatment alternative can be recognized. External applicants (e.g. manufacturers of medical devices) can also apply for a testing procedure by submitting informative documents to the G-BA on the potential of the method. The determination of the potential of a method is the responsibility of the G-BA, which has specified criteria for this purpose [271]. The G-BA usually commissions the Institute to evaluate testing applications according to §137e (7) SGB V in view of whether a potential of the method can be inferred from the application documents.

With the Promotion of Health Care Act, in 2015 an assessment of new examination and treatment methods (NUB[5]) with high-risk medical devices was introduced via §137h SGB V. This assessment refers to methods that a) follow a new theoretical-scientific concept [108,271], b) are particularly invasive [108,271], and c) lead to a first request according to §6 of the Hospital Reimbursement Act ("NUB request"). The G-BA receives documents on such methods from hospitals and medical device manufacturers. The G-BA generally commissions the Institute to assess documents according to §137h SGB V in respect of whether a benefit or harmfulness or ineffectiveness can be recognized in them.

Due to the Promotion of Health Care Act, in 2015 §139b SGB V was extended by Paragraph 5. §139b (5) SGB V specifies that insured persons and other interested individuals can propose assessments of medical examination and treatment methods for selected diseases as well as assessments of questions of the quality and efficiency of services provided within the framework of SHI. According to §139b (5) SGB V, this excludes topic proposals where the focus is on the separate assessment of a drug. It is IQWiG's task to select topics from these proposals that are particularly important for the health care of patients and for which health

[5] Neue Untersuchungs- und Behandlungsmethoden

technology assessment (HTA) reports commissioned by IQWiG are then produced (see Chapter 6).

With the Digital Health Care Act (DVG[6]), §139b (3) SGB V was supplemented with the new No. 3 and §139b SGB V with Section 6. This passage stipulates that the Association of the Scientific Medical Societies (AWMF[7]) can propose clinical practice guidelines to the Federal Ministry of Health for which IQWiG is to support guideline development or updating with evidence searches.

According to §139a (4) Sentence 1 SGB V, the Institute is legally obliged to ensure the "assessment of the medical benefit [of interventions] following the internationally recognized standards of evidence-based medicine and the economic evaluation following the relevant internationally recognized standards for this purpose, in particular of health economics". Depending on the commission, the Institute determines the methods and criteria for the preparation of assessments on the basis of the international standards of evidence-based medicine (EBM) and health economics recognized by the relevant experts. The term "evidence-based medicine", its development and the underlying concept are described in detail in Section 1.3. The term "health economics" and the underlying concept are described in detail in Section 1.4.

During the preparation of its reports, the Institute ensures the high transparency of procedures and appropriate involvement of third parties. In all important phases of report preparation, the law obliges the Institute to provide the opportunity of comment to experts, manufacturers and relevant organizations representing the interests of patients and self-help groups of chronically ill and disabled persons, as well as to the Federal Government Commissioner for Patients' Affairs. The Institute goes beyond this obligation by allowing all interested persons and institutions the opportunity to submit comments on its reports, and considers these comments in its assessments.

The implementation of these regulations is described in Section 2.2.5.

In addition, the Institute publishes the results of its work and supplementary information on its publicly accessible website. Those interested can also subscribe to the Institute's e-mail service (info service), where subscribers themselves can specify what type of information they would like to receive from the Institute.

1.2 General commission of the G-BA

In December 2004, the G-BA awarded IQWiG a so-called general commission [272]. With the general commission, the Institute was commissioned "to continuously monitor and assess medical developments of fundamental importance and their effects on the quality and efficiency

[6] Digitale-Versorgung-Gesetz

[7] Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

of medical care in Germany by identifying and assessing the relevant literature, and to inform the G-BA regularly about these developments. With this commission, the G-BA assumes that the Institute will not only process individual commissions from the G-BA in the fields of work assigned to the Institute under §139a (3) SGB V, but will also, on the basis of its independent scientific work, provide the G-BA with information on medical developments relevant to health care that is necessary for the G-BA's statutory tasks, and will develop concrete proposals for individual commissions that the Institute considers relevant against the background of this information."

In July 2006 and March 2008, the general commission was further specified and adapted with regard to the production of health information [273]. IQWiG "produces and publishes information on its own responsibility within the framework of its scientific work, without the need for an individual commission in each case. The Institute for Quality and Efficiency in Health Care is solely responsible for the content of the information, including any consequences arising from it."

1.3 Evidence-based medicine

EBM refers to patient health care that is not only based on opinions and consensus, but considers evidence – i.e. proof (e.g. of the benefit of a medical intervention) determined with the most objective scientific methods possible. EBM comprises tools and strategies designed to safeguard against false decisions and false expectations. In this context, a false decision can mean that beneficial interventions are not implemented in health care (or implemented with delay), or that useless or even harmful interventions are widely applied [24,232,301,303].

However, tools designed to prevent subjective (and therefore often biased) assessments (see also Section 7.13) were not first invented with the introduction of the term EBM, but originated decades ago. In Germany, as early as 1932 Paul Martini described the main elements of a fair assessment of drug effectiveness in his monograph *Methodology of Therapeutic Studies* [492]. In the early 1960s, the method of randomly allocating study participants to comparator groups (randomization) in order to assess the effectiveness and safety of medical interventions became the internationally accepted standard [352]. Starting in the United States, in this period this type of study became the precondition for the approval of drugs and (in some cases) medical devices regulated by authorities, legislation and other regulations [41]. About 20 years later, clinical epidemiologists attempted to establish this methodology in clinical practice [238]. Accompanied at times by serious controversy, this was not actually achieved until the 1990s, at the same time as the concept was defined as EBM. Since this time, clinical studies and the systematic search for and assessment of these studies (systematic reviews) have formed the basis of the international scientific standard for HTAs [39].

EBM is not a rigid concept: which standard tool is to be applied, and when, depends on the question to be answered and the decision to be made. Despite the application of standards, decisions for which no international specifications are (as yet) available have to be made repeatedly in the search for, and the processing and assessment of studies. EBM also includes

the freedom to define one's own specifications in such situations. However, this freedom is linked to the obligation to define such specifications preferably a priori, and to explain assessments in a transparent manner, so that the rationale is comprehensible. The following sections explain that in the implementation of EBM and the definition of specifications, an institution such as IQWiG is in a different situation from clinicians seeking support for a treatment decision.

1.3.1 Practical evidence-based medicine

The EBM concept is a strategy for physicians who, from a range of possible interventions, seek the most promising alternatives suited best to the needs of their patients, and who aim to offer prospects of success in an objective manner. This implementation of EBM in daily clinical practice for individual patients was defined by David Sackett et al. [607] as follows: "EBM is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research" (1996).

However, the "best available evidence" is often incomplete or unreliable. EBM has developed instruments to assess uncertainty; evidence levels are often used for illustration. In this way, EBM helps physicians and patients to recognize the type and degree of uncertainty; they can then discuss how to deal with this. Especially in uncertain situations, personal preferences are important and determine what option patients choose. Apart from being based on evidence, decisions are also ideally based on the clinical condition and circumstances of the individual patient, as well as on his or her preferences and actions [342]. At the same time, the description of the identified gaps in knowledge creates the precondition for medical research targeted towards patients' needs.

EBM is based on a critical approach [431]. The importance of scepticism is underlined by the fact that over the past few decades, several insufficiently tested but widely applied therapies have been assessed with EBM methods; these assessments have shown that a hasty, overoptimistic approach to a new intervention can have dangerous consequences for patients [197,588]. It is the Institute's task to assess objectively with what certainty the benefit of medical interventions has been demonstrated, in order to counter inappropriate judgements.

1.3.2 The relevance of evidence-based medicine for the Institute

The Institute's main task is to provide the most reliable answer possible to the question specified by the contracting agency as to whether evidence is available of the benefits or harms from an intervention. The aim is to present sufficiently reliable proof that "Treatment A" is better for patients than "Alternative B" for a specific disease. In short: What is the benefit of A compared with B?

This remit of the Institute is therefore intentionally not aimed towards treating individual patients with their potential specific characteristics, but towards determining for which patient

groups proof of a benefit of an intervention is available. The corresponding reports of the Institute serve as a basis for the G-BA for decisions that apply in principle to all persons insured by statutory health insurance. In its decisions, the G-BA in turn then considers, among other things, aspects of patient care that are beyond the scope of a benefit assessment [271].

1.3.3 Strategies of evidence-based medicine

A characteristic standard element of EBM is the structured and systematic approach to the search for a response to a medical question:

1) The medical question must be worded precisely. Medicine (nearly) always deals with the choice between at least 2 alternatives. This can refer to treatments, diagnostic tests or complex changes in life style. From this, the following question is always inferred: Is Option A better than Option B? In this context, the decision not to undergo treatment can also be an option that should be thoroughly reviewed. However, it should be stressed that such an option (e.g. watchful waiting [383]) is not the same as doing nothing.
2) It must be defined how the benefit of treatment (or diagnosis or lifestyle change) should be measured. A standard element of EBM is the question about relevant consequences for patients: Can life expectancy be increased? Can symptoms and quality of life be improved?
3) In EBM it is explicitly noted that in medicine, only probability statements or only conclusions about groups of patients are usually possible with regard to the benefit of treatment, diagnostic procedures, or lifestyle changes. Benefit is demonstrated by showing that an intervention increases the probability of a beneficial outcome and/or reduces the risk of a non-beneficial outcome. In order to prove the benefit of an intervention, studies in sufficiently large groups of suitable patients are required. International researchers have developed a range of rules and tools for the planning, conduct, and analysis of such studies. The most important aim is to minimize (or, if this is impossible, at least document) factors that can distort the results of a comparison. The effects of such confounding factors are referred to as “bias”. The rules and tools that are internationally accepted as the prevailing standard, and are under continuous development, are the methodological basis of EBM and the Institute’s work.
4) A further key EBM strategy is to identify all “appropriate” studies (i.e. whose design and conduct are of appropriate quality) on a question and, in this way, to summarize the reliable evidence available. In this context, if large differences are shown between the results of individual studies (heterogeneity), an attempt should be made to explain them. The findings of these summaries and assessments are referred to as systematic reviews; the statistical analyses are referred to as meta-analyses.

1.3.4 The relevance of certainty of results

A specific characteristic of EBM is that it allows assessment as to what extent the available evidence is reliable. Decisions made by the G-BA must be based on highly reliable scientific

evidence, as they have far-reaching consequences for all SHI members (e.g. exclusion of services from reimbursement).

The assessment of the certainty of results therefore plays a key role in the Institute's reports. Numerous details on how studies are planned, conducted, analysed, and published have an impact on how reliable the available results are. It is an international EBM standard to test and assess these aspects critically. However, how the certainty of results needed to answer a question can be achieved also depends on the disease and on the effect size of an intervention: If 2 athletes pass the finishing line of a fair race with a great distance between them, no stopwatch is needed to identify the winner. For example, the benefit of a new therapy that results in the cure of a previously always fatal disease can be proven by a relatively small number of surviving patients. In this case, the judgement is also ultimately based on a comparison, but in interventions with such dramatic effects, the comparison between historical and current patients may already provide sufficient certainty. However, therapies that show such dramatic benefits are very rare in modern medicine [339].

In chronically ill patients in particular, differences between 2 therapy alternatives are mostly smaller and may be easily confounded by a fluctuant course of disease. In these cases, precise methods and appropriate study designs are required in order to be able to recognize therapy effects under such fluctuations.

It can be assumed that the Institute will be specifically commissioned to compare such interventions where it is not immediately recognizable which alternative will be more beneficial. However, the smaller the expected differences between 2 alternatives are, the more reliable the studies must be in order to be sufficiently certain that an observed effect is not caused by chance or measurement errors (a world record in a 100 metre race can no longer be measured with an hourglass). In the event of small differences, their clinical relevance must also be judged.

The following requirements for precision and reliability determine the Institute's mode of operation:

1) For every question investigated, it is an international EBM standard to specify the study type (measuring tool) that minimizes the risk of unjustifiably discriminating against one of the alternatives.
2) The Institute's assessments on the benefits and harms of interventions are therefore normally based only on studies with sufficient certainty of results. This ensures that the decisions made by the G-BA, which are based on the Institute's recommendations, are supported by a sound scientific foundation. Moreover, an assessment that includes a literature search for studies with insufficient certainty of results would be costly and time consuming.

3) If it emerges that studies of the required quality and precision are generally lacking, it is the core task of the Institute to describe the circumstances and conclude that on the basis of the "currently best available" evidence, it is not possible to make reliable recommendations.

4) It is the G-BA's responsibility to take this uncertainty into account in its decision-making processes. In addition to considering scientific evidence, the G-BA also considers other aspects in its decisions, such as the efficiency of interventions as well as the needs and values of people [292]. In an uncertain scientific situation, such aspects become more important. In addition, the G-BA also has the option to call for or initiate studies in order to close the evidence gaps identified.

1.3.5 The connection between certainty of results and proximity to everyday conditions

The great value placed on the assessment of the certainty of results is often criticized. One argument is that studies with a high certainty of results (especially randomized controlled trials, RCTs) may have high internal validity, but often do not represent patient care under everyday conditions, and are therefore not transferable, i.e. have only low external validity. In this context it must be examined how well the patient population investigated in the studies, the interventions applied, and the outcome criteria analysed are in accordance with everyday conditions in health care. This criticism is then often connected to the call to include other study types without randomization, in order to better consider everyday conditions.

However, this criticism conflates levels of arguments that should be clearly separated. The following aspects should be taken into account:

1) The basis of a benefit assessment is the demonstration of causality. An indispensable precondition for such a demonstration is a comparative experiment, which has to be designed in such a way that a difference between intervention groups – an effect – can be ascribed to a single determining factor – the intervention tested. This goal requires considerable efforts in clinical trials, as there are numerous confounding factors that feign or mask effects (bias). The strongest of these distorting influences are unequal baseline conditions between comparator groups. Randomization (together with careful concealment) is currently the best available tool to minimize this type of bias. Random allocation of participants to groups ensures that there are no systematic differences between groups, neither regarding known factors (e.g. age, gender, disease severity), nor unknown factors. For this reason, RCTs provide a basic precondition for the demonstration of causality. However, randomization alone does not guarantee high certainty of results. To achieve this, the unbiased assessment, summarization and publication of results, for example, are also required.

2) Study types other than RCTs are usually not suited to demonstrate causality. In non-randomized comparative studies, as a matter of principle structural equality of groups cannot be assumed. They therefore always provide a potentially biased result and mostly cannot answer with sufficient certainty the relevant question as to whether a difference observed is caused by the intervention tested. The use of non-randomized studies as proof of the causality of an intervention therefore requires particular justification or specific preconditions and special demands on quality.
3) It is correct that many randomized studies do not reflect aspects of everyday patient care, for example, by excluding patients with accompanying diseases that are common in everyday life. However, this is not a consequence of the randomization technique, but of other factors (e.g. definition of narrow inclusion and exclusion criteria for the study, choice of interventions or outcome criteria). In addition, patients in randomized studies are often cared for differently (more intensively and more closely) than in everyday practice. However, these are intentional decisions made by those persons who wish to answer a specific question in a study. Dispensing with randomization does not change these decisions. There is also a selection of participants in non-randomized studies through inclusion and exclusion criteria and other potential design characteristics, so that external validity is not given per se in this study type any more than in RCTs.
4) Even if patient groups in an RCT differ from everyday health care, this does not mean the external validity of study results must be questioned. The decisive issue is in fact whether it is to be expected that a therapy effect determined in a population varies in a different population.
5) It depends on the individual case how the intensity of care provided in a study influences outcomes. For example, it is conceivable that a benefit of an intervention actually exists only if patients are cared for by specially qualified physicians, as under everyday conditions too many complications may otherwise occur. However, it is also possible that intensified care of patients is more likely to reduce differences between groups. For example, differences in treatment adherence may be smaller in studies where, as a matter of principle, patients are cared for intensively.
6) However, the initiators of a clinical trial are responsible for the specification of study conditions. They can define research questions and outcomes rated as so relevant that they should be investigated in a study. If, for example, a drug manufacturer regards treatment adherence to be an important aspect of the benefit of a product, the obvious consequence would be to initiate studies that can measure this aspect with the greatest possible certainty of results and proximity to everyday conditions, and at the same time demonstrate its relevance for patients.

The above remarks show that certainty of results and proximity to everyday conditions (or internal and external validity) have no fixed relationship. High certainty of results and proximity to everyday conditions do not exclude one another, but only require the appropriate combination of study type, design and conduct.

Even if criticism of the lack of proximity to everyday practice may actually be justified for many studies, nothing would be gained by dispensing with high certainty of results in favour of greater proximity to everyday practice, because one would thereby be attempting to compensate one deficit by accepting another, more serious, one [340].

Studies that combine proximity to everyday conditions and high certainty of results are both desirable and feasible. RCTs are indeed feasible that neither place demands on patients beyond everyday health care nor specify fixed study visits. Such studies are being discussed at an international level as real world trials, practical trials or pragmatic trials [254,258,283,450,714]. However, such so-called pragmatic trials may themselves also lead to interpretation problems. For example, if very broad inclusion criteria are chosen, the question arises as to whether the (overall) study results can be applied to the overall study population [758], which, at least to some extent, would ultimately have to be answered by means of appropriate subgroup analyses.

1.3.6 Benefit in individual cases

The aim of a benefit assessment is to make robust predictions for future patients using results of studies suited to demonstrate causal effects. The conclusions drawn always apply to groups of patients with certain characteristics. Conclusions on the benefit of an intervention in terms of predictions of success for individual cases are, as a matter of principle, not possible. Vice versa, experiences based on individual cases (except for specific situations, e.g. dramatic effects) are unsuitable for a benefit assessment, as it is not possible to ascribe the results of an individual case (i.e. without a comparison) to the effect of an intervention.

For certain research questions (therapy optimization in individual patients) so-called (randomized) single patient trials (or N-of-1 trials) can be conducted [302,304,413,627]. However, these are usually not suited to assess the benefit of a treatment method for future patients.

1.4 Health economics

Two issues can be expressed with the term “health economics”.

In the wider sense it is about “the analysis of economic aspects of the health care system using concepts of economic theory” [630]. For this purpose, among other things, concepts are used from the areas of microeconomic behavioural theory, competition theory, economic theory of politics, and management theory [630]. The subject of such a study could be, for example, how players in the health care system change their behaviour after the setting of incentives (e.g. out-of-pocket costs) or whether the results of price negotiations following the Act on the Reform of the Market for Medicinal Products (AMNOG[8]) actually prevent excessive prices for new drugs. It can be discussed both from a methodological and from an ethical point of view to what

[8] Arzneimittelmarktneuordnungsgesetz

extent such studies can and should be used to steer the health care system, but this is not a subject of this short presentation.

In the narrower sense, health economics is here viewed to be an HEE as a comparative analysis and a budget impact analysis (BIA) as a non-comparative analysis [200]. These analyses serve, among others, to inform decision makers on the cost-effectiveness ratios of interventions and, besides the benefit assessment of interventions, thus represent an area of HTA.

1.4.1 Relevance of health economics for the Institute

With the establishment of the Institute in 2004, the G-BA and the Federal Ministry of Health were free to commission an HEE. Until the change in the law in 2007, an HEE of drugs was not intended. With the SHI Act to Promote Competition[9] the HEE of drugs was anchored in §35b SGB V to gain information on the recommendation for a so-called ceiling price. New drugs were to be reimbursed up to this ceiling price, as this price was to represent the appropriate costs for the added benefit of a new drug in comparison with other drugs and treatment forms in a therapeutic indication. The precondition for the commissioning of an HEE was thus to be proof of the added benefit of a drug, which had to have been shown in the form of an IQWiG benefit assessment.

With AMNOG, which became effective on 1 January 2011, the relevance of the HEE shifted within the procedure of the early benefit assessment of drugs. An HEE is primarily intended for cases where price negotiations fail between the SHI umbrella organization[10] and pharmaceutical companies and where no agreement is reached in the subsequent arbitration procedure. However, the question of the HEE remains: according to §35b (1) Sentence 4 SGB V in connection with the 5th Chapter §32 (3) of the G-BA's Code of Procedure [271], the appropriateness and reasonableness of cost coverage by the community of SHI insurants must be considered. For the G-BA to consider these factors in an appropriate manner, it must receive the corresponding information. This information is provided by the HEE (appropriateness) and the budget impact analysis (reasonableness). The assessment of the appropriateness and reasonableness of cost coverage is conducted with regard to whether, under observance of the principle of proportionality, a justifiable relation between the costs and the benefit of the drug exists. In this context, according to the 5th Chapter §32 (2, 3) of the G-BA's Code of Procedure, IQWiG is to present a recommendation on the basis of which the G-BA is to make a decision [271]. The presentation of a justifiable relation between the costs and the benefit must thus ensue from the HEE.

[9] Gesetzliche-Krankenversicherung(GKV)-Wettbewerbsstärkungsgesetz

[10] Spitzenverband Bund der Krankenkassen, GKV-Spitzenverband

1.4.2 International standards of health economics

As in every science, international standards also exist in health economics. These include the classification of HEE into the study types of cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis (in the narrower sense) [200].

International standards also exist for the methods applied in HEE. With regard to the benefit assessment, the Institute follows the principles of EBM and the resulting methodological approaches that are established as the corresponding international standards. Before one speaks of international standards in health economics, one must distinguish between clearly methodological questions and questions based on value judgements, opinions or surveys. This can be illustrated using the example of the discounting rate. With a discounting rate, benefits and costs incurred in different periods are discounted to one period so that they are comparable for a decision. The pure performance of discounting is clearly regulated mathematically and thus a methodological question. The choice of discounting rate and particularly the decision as to whether the costs and benefits are to be discounted with the same rate or possibly even with a non-constant rate is, among other things, subject to issues concerning the appraisal of the future economic development and intergenerational fairness and is thus a value judgement [138,335,523,534,539,553,571].

As shown by internationally recognized instruments for the evaluation of health economic analyses [134,199,368,560], there are many steps and aspects for which methodological requirements exist and which must be processed in a transparent and comprehensible way. These include, among others:

- Definition of the interventions under assessment and their comparators. A choice must be justified to prevent wrong decisions on the basis of an interest-driven choice of comparators.
- Perspective of the HEE.
- Time horizon of the HEE.
- Type of study (see above) with justification.
- Costs with presentation of resource use and resource evaluation.
- Adjustment for inflation and conversion of currency (if necessary).
- Development and explanation of the model and preferably also justification of the choice of model, e.g. decision tree, Markov model.
- Discounting rate.
- Presentation of results, e.g. in an aggregated or a disaggregated form.
- Investigation of the uncertainty of results by means of deterministic and probabilistic sensitivity analyses.

- Presentation of uncertainty, e.g. with cost-effectiveness-acceptance curves or the net benefit.

In this respect, requirements for good methodological practice are available in textbooks and also, for example, in the guidelines of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

1.4.3 Methodological standards in health economics

Furthermore, other aspects of an HEE are also understood to be the international standard. For instance, in the health care system a decision based on a threshold per quality-adjusted life year (QALY) gained is often presented as the international standard in health economics. However, this should be seen critically. On the one hand, the vast majority of countries in which HEEs contribute to decision-making do not have a (fixed) threshold [256,638]. On the other, this would be a value judgement, and would thus not fall under the international methodological standards following §139a (4) Sentence 1 according to which only methodological standards apply in the assessments of the Institute.

Furthermore, the question of the measure of overall benefit arises not only as a methodological question, but also always under the aspect of a value judgement. In this context, the research question and aim of a health economic analysis have an influence on which instrument should be used as a measure of overall benefit. This also means that the question as to whether the QALY should be used must be highlighted under ethical, legal, and cultural aspects. In turn, from a scientific or methodological point of view it can be discussed which assumptions are considered in the QALY concept, for example, the assumption that the assessment of a state is independent of its duration (= constant proportional [time] trade off), and whether these assumptions are sustainable. Likewise, it can be investigated methodologically whether the various measurement methods applied (e.g. indirect versus direct) lead to different results and how this difference can be interpreted. A question of value judgement on the basis of legal requirements (e.g. SGB V) is again the question in which persons the utility values to generate QALYs should be elicited; in those actually affected by a disease or in the general population.

Ultimately, the following question needs to be raised: How should resources in the health care system be distributed? That is, on the basis of which rights, claims or needs, with which aim, and which impact on the allocation of goods or services? This question is only understood as a value judgement, and this in turn determines which scientific standards and methods should be applied.

2 The Institute's products

According to its legal remit, the Institute prepares a variety of products in the form of scientific reports and easily understandable health information for consumers and patients. This chapter describes procedures and general methods applied in the preparation of the Institute's products. At first the individual products are named and product-specific procedures presented (Section 2.1). The next section outlines further aspects independent of products (Section 2.2).

2.1 Product-specific procedures

The Institute‘s products include

- report
- rapid report
- dossier assessment
- HEE according to §35b SGB V
- assessment of potential
- assessment according to §137h SGB V
- addendum
- health information
- working paper
- HTA report
- evidence report

The preparation of reports and rapid reports is conducted on the basis of the award of individual commissions through the G-BA or Federal Ministry of Health. The basis of this are the Institute's responsibilities described in §139a SGB V (see Section 1.1). The main difference between reports and rapid reports is that a public commenting procedure (hearing) is only conducted for reports, but not for rapid reports. Accordingly, rapid reports are particularly intended for recommendations at short notice, for which, from the point of view of the contracting agency, no hearings by the Institute are required.

Dossier assessments are commissioned by the G-BA. The foundation for this is §35a SGB V, which regulates the assessment of the benefit of new active ingredients on the basis of a dossier by the pharmaceutical company (see also Section 3.3.3). No hearing by the Institute is intended for dossier assessments according to §35a SGB V. A commenting procedure is conducted in the further process by the G-BA.

Furthermore, according to §35b SGB V, the Institute can be commissioned by the G-BA to conduct HEEs of drugs. For such evaluations, it is intended that IQWiG conducts hearings. A further commenting procedure is conducted at the G-BA.

Assessments of potential are commissioned by the G-BA and refer to applications for testing according to §137e SGB V. No hearing by the Institute is intended. If a testing is performed, the G-BA conducts a commenting procedure on the testing directive.

Assessments according to §137h SGB V are commissioned by the G-BA and refer to new examination and treatment methods with high-risk medical devices. No hearing by the Institute is intended. If a directive is decided on, the G-BA conducts a commenting procedure in this regard.

Addenda can be commissioned by the G-BA or Federal Ministry of Health in cases where, after the completion of a product, the need for additional work on the commission arises during the course of consultations.

Health information can be prepared on the basis of an individual commission; it can also be the consequence of a commission in other areas of the Institute's work (easily understandable version of other products of the Institute, e.g. a report) or be prepared within the framework of the general legal remit to provide health information.

Working papers are prepared under the Institute's own responsibility; specific commissioning by the G-BA or Federal Ministry of Health is not required. This takes place either on the basis of the general commission (see Section 1.2), with the aim of providing information on relevant developments in health care, or within the framework of the legal remit to develop the Institute's methods. The Institute's *General Methods* are not to be understood as a working paper in this sense, and are subjected to a separate preparation and updating procedure, which is outlined in the preamble of this document.

HTA reports are produced on topics proposed by insured persons or other interested individuals. The Institute selects topics from the proposals that are particularly important for the health care of patients in Germany. In this context, the perspectives of both consumers and patients as well as the scientific perspective are considered. HTA reports on the selected topics are produced. This is based on §139b (5) SGB V. A hearing by the Institute is intended for the HTA reports.

An evidence search according to §§139 (3) No. 3, 139b (6) SGB V includes the production of several evidence reports to support the development or updating of a clinical practice guideline by the AWMF and is commissioned by the Federal Ministry of Health. There is no provision for a commenting procedure.

An overview of the Institute's various products is shown in Table 1 below. Product-specific procedures are described in the subsequent Sections 2.1.1 to 2.1.11

Table 1: Overview of the Institute's products

Product	Objective	Procedure	Commissioned by
Report	Recommendations on tasks described in §139a SGB V, including hearing	Described in Section 2.1.1	G-BA, Federal Ministry of Health
Rapid report	Recommendations on tasks described in §139a SGB V, insofar as no hearing is required; in particular provision of information at short notice on current topics	Described in Section 2.1.2	G-BA, Federal Ministry of Health
Dossier assessment	Assessment of the benefit of drugs with new ingredients according to §35a SGB V	Described in Section 2.1.3	G-BA
Health economic evaluation according to §35b SGB V	Assessment of the relation of the cost and benefit of drugs according to §35b SGB V, including a hearing	Described in Section 2.1.4	G-BA
Assessment of potential	Assessment of the potential of new examination and treatment methods according to §137e SGB V	Described in Section 2.1.5	G-BA
Assessment according to §137h SGB V	Assessment of the benefit, harmfulness or ineffectiveness of new examination and treatment methods with high-risk medical devices according to §137h SGB V	Described in Section 2.1.6	G-BA
Addendum	Supplementary information provided at short notice by the Institute on issues that have arisen during the consultation on its completed products	Described in Section 2.1.7	G-BA, Federal Ministry of Health
Health information	Easily understandable information for consumers and patients; wide scope of topics	Described in Section 2.1.8	General commission of the G-BA
Working paper	Information on relevant developments in health care or methodological aspects	Described in Section 2.1.9	General commission of the G-BA
HTA report	Assessment of medical examination and treatment methods according to §139b (5) SGB V, including a hearing	Described in Section 2.1.10	Initiation by the Institute on the basis of proposals of interested individuals
Evidence report	Evidence presentation according to §§139a (3) No. 3, 139b (6) SGB V	Described in Section 2.1.11	Federal Ministry of Health
G-BA: Gemeinsamer Bundesausschuss (Federal Joint Committee); HTA: health technology assessment; SGB V: Sozialgesetzbuch Fünftes Buch – Gesetzliche Krankenversicherung (Social Code Book V – Statutory Health Insurance)			

2.1.1 Report

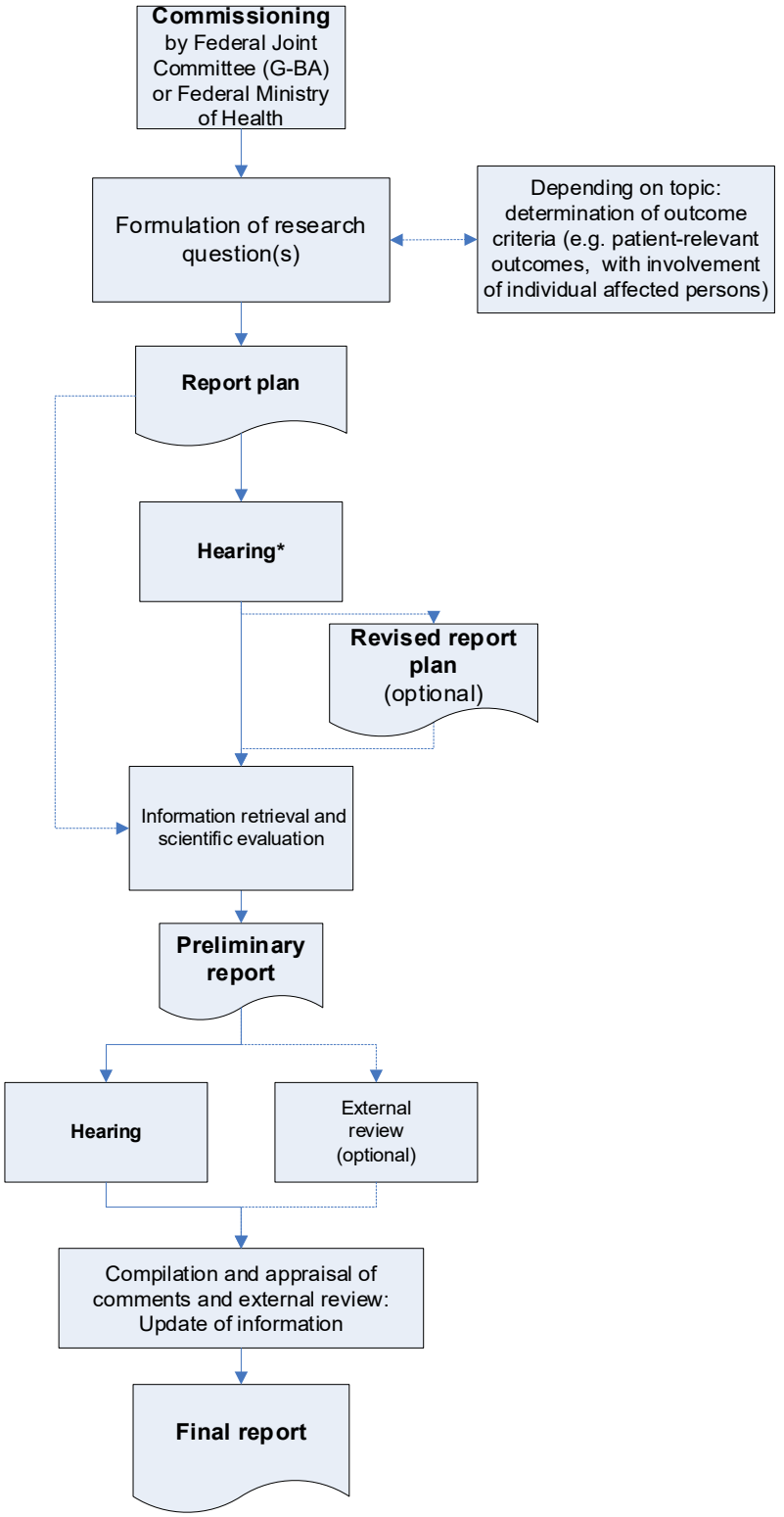
The procedure for report production is presented in Figure 1. All working steps are performed under the Institute's responsibility and regularly involve external experts (see Section 2.2.2). If necessary, the Institute's Scientific Advisory Board is also involved. The internal quality assurance process is not outlined in this flow chart.

After **commissioning** by the G-BA or Federal Ministry of Health, the research question is formulated. Depending on the topic, the determination of outcome criteria is also required (e.g.

in benefit assessments). As a rule, affected persons are involved, especially in the definition of patient-relevant outcomes. Affected persons may include patients (potentially represented by their parents or other relatives) as well as potential participants in prevention measures. Subsequently, the report plan (protocol) is prepared.

The **report plan** forms the basis for the production of the preliminary report and contains the precise scientific research question, including the outcome criteria (e.g. patient-relevant outcomes), as well as the inclusion and exclusion criteria of the information to be used in the assessment. This plan also includes a description of the project-specific methodology applied in the retrieval and assessment of information. The report plan is first forwarded to the contracting agency as well as to the Foundation's Board of Directors, the Foundation Council and the Board of Trustees. It is normally published on the Institute's website 5 working days later.

A hearing on the report plan is conducted according to the legal regulations in §139a (5) SGB V. The hearing is conducted by means of **written comments**, which can be submitted within a period of at least 4 weeks from the time of notification on the Institute's website. The hearing particularly refers to the project-specific methodological approach applied to answer the research question. The research question itself is usually specified by the commission, and is not an object of the hearing.



*A hearing procedure for the report plan is conducted according to the legal regulations in §139a (5) SGB V.

Figure 1: Procedure for the production of a report

The comments are analysed and published in order to document the hearing. If no change in the methodology of the report is required, the documentation of the hearing is published together

with the preliminary report. If a change in the methodology of the report is required, a revised new version of the report plan is prepared, which is first forwarded to the contracting agency, the Foundation's Board of Directors, the Foundation Council and Board of Trustees, together with the documentation of the hearing on the report plan. This document is usually published on the Institute's website 5 working days later. The revised version of the report plan is the basis for the preparation of the preliminary report.

The results of the information retrieval and the scientific assessment are presented in the **preliminary report**. In order to avoid undue delay in the Institute's work, the retrieval and assessment of information already start before completion of the hearing on the report plan on the basis of the criteria formulated in the report plan. However, the result of the hearing is explicitly not anticipated, as these criteria may be modified on grounds of the hearing on the report plan. This may also lead to supplementation and/or modification of the retrieval and assessment of information.

The preliminary report includes the preliminary recommendation to the G-BA. After completion, it is first forwarded to the contracting agency as well as to the Foundation's Board of Directors, the Foundation Council and the Board of Trustees. The preliminary report is usually published on the Institute's website 5 working days after it is sent to the contracting agency.

The preliminary report is subject to a hearing. As a matter of principle, the hearing is conducted by means of **written comments**, which can be submitted within a period of at least 4 weeks from the time of notification on the Institute's website. Optionally, an oral scientific debate with those submitting comments may be held. This debate serves the potentially necessary clarification of aspects of the written comments. The hearing in particular refers to the results of the retrieval and assessment of information presented in the preliminary report.

The **final report**, which is based upon the preliminary report and contains the assessment of the scientific findings (considering the results of the hearing on the preliminary report), represents the concluding product of the work on the commission. The final report and the documentation of the hearing on the preliminary report are first forwarded to the contracting agency, the Foundation's Board of Directors, the Foundation Council as well as the Foundation's Board of Trustees. These documents are then published on the Institute's website (usually a further 4 weeks later). If comments are received on final reports containing substantial evidence not considered, or if the Institute receives information on such evidence from other sources, the contracting agency will be sent well-founded information on whether, in the Institute's opinion, a new commission on the topic is necessary (if appropriate, a report update) or not. The contracting agency then decides on the commissioning of the Institute. Such an update is conducted according to the general methodological and procedural requirements for the Institute's products.

If an examination or treatment method is assessed according to §139a (3) No. 1 SGB V, the final report is to be completed within one year after the award of the commission, according to §4 of the Regulation on Procedures for the Assessment of Methods (MBVerfV[11]) [107].

2.1.2 Rapid report

The procedure for the production of a **rapid report** is presented in Figure 2. All working steps are performed under the responsibility of the Institute, involving external experts where appropriate (see Section 2.2.2). If necessary, the Institute's Scientific Advisory Board is also involved. The internal quality assurance process is not presented in this flow chart.

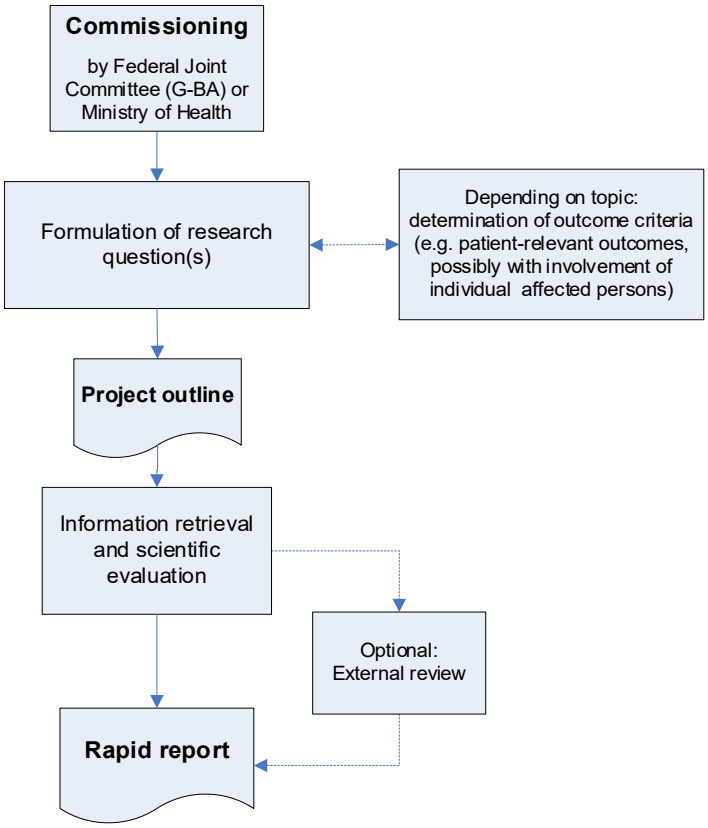


Figure 2: Procedure for the production of a rapid report

Rapid reports are primarily produced with the aim of providing information at short notice on relevant developments in health care (e.g. new technologies, publication of milestone studies). A shorter production period is usually required here. Therefore, no hearings are conducted during the course of the project.

After **commissioning** by the G-BA or Federal Ministry of Health, the research question is formulated. Depending on the topic, the determination of outcome criteria is also required (e.g. in benefit assessments). In this context, the opinion of affected individuals can be sought,

[11] Methodenbewertungsverfahrensverordnung

especially for the definition of patient-relevant outcomes. Subsequently, the project outline is prepared.

The **project outline** summarizes the main steps of the information retrieval and scientific assessment. It forms the basis for the production of the rapid report. The project outline is not published.

The **rapid report** presents the results of the information retrieval and scientific assessment. Before completion, as a further quality assurance step, optionally a draft of the rapid report may be reviewed by one or more external reviewers (see Section 2.2.4) with proven methodological and/or topic-related competence. After completion the rapid report is then sent to the contracting agency, the Foundation's Board of Directors and Foundation Council, as well as (usually a week later) to the Board of Trustees. The rapid report is usually published on the Institute's website 4 weeks after it is sent to the contracting agency and Board of Directors. If comments on rapid reports are received that contain substantial evidence not considered, or if the Institute receives such evidence from other sources, the contracting agency will be provided with well-founded information on whether, in the Institute's opinion, a new commission on the topic is necessary (if appropriate, a rapid report update) or not. The contracting agency then decides on the commissioning of the Institute. Such an update is conducted according to the general methodological and procedural requirements for the Institute's products.

2.1.3 Dossier assessment

The procedure for the production of a dossier assessment is presented in Figure 3. All working steps are performed under the Institute's responsibility and regularly involve external expertise (see Section 2.2.2). If necessary, the Institute's Scientific Advisory Board is also involved. The internal quality assurance process is not outlined in this flow chart.

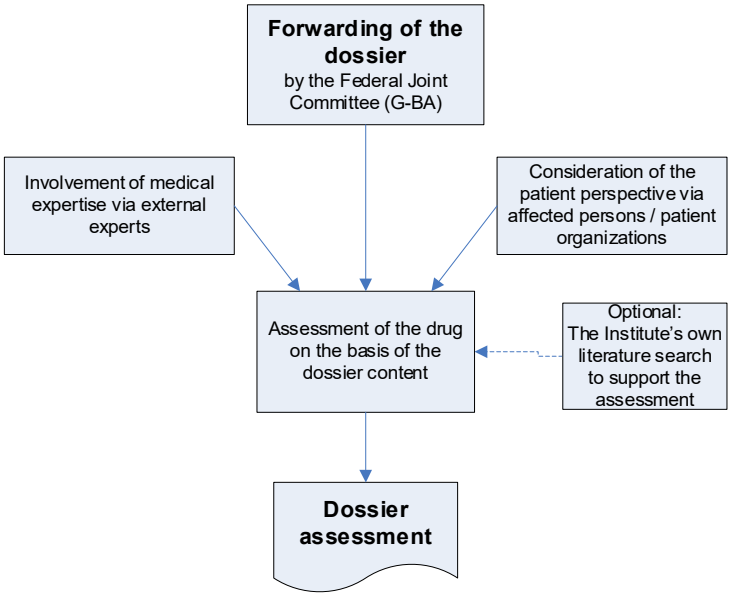


Figure 3: Procedure for the production of a dossier assessment

After the **forwarding of the dossier** by the G-BA, the assessment of the dossier content is conducted under the responsibility of the Institute. In this context, medical expertise and the patient perspective are as a rule involved via external experts and affected persons/patient organizations respectively.

Medical expertise is primarily involved on the basis of a questionnaire sent to external experts at the beginning of the assessment. In its assessment the Institute considers the external experts' feedback. In addition, external experts may if necessary be drawn upon to clarify specific questions arising during the course of the assessment. External experts are identified via the Institute's own database for external experts (see Section 2.2.2).

The **patient perspective is considered** on the basis of a questionnaire sent to affected persons/patient organizations at the beginning of the assessment. In its assessment the Institute considers the information provided in this questionnaire, e.g. on relevant outcomes and important subgroups. Affected persons/patient organizations are identified via the relevant organizations named in §140f SGB V.

The basis of the assessment is the dossier submitted to the G-BA by the pharmaceutical company and then forwarded to the Institute. The Institute may optionally perform its **own literature search** to support the assessment.

The preparation of the **dossier assessment** is the final step in the process. In accordance with §35a SGB V, the assessment must be completed no later than 3 months after the relevant date for the submission of the dossier. After its completion, the dossier assessment is delivered to the G-BA. Shortly afterwards the Foundation's Board of Directors, the Foundation Council and the Foundation's Board of Trustees are informed about the delivery and the dossier assessment is published on the Institute's website.

2.1.4 Health economic evaluation according to §35b SGB V

The procedure for an HEE according to §35b SGB V is presented in Figure 4. All working steps are performed under the Institute's responsibility. The procedure regularly involves external experts. If necessary, the Institute's Scientific Advisory Board may also be involved. The internal quality assurance process is not outlined in this flow chart.

Before **commissioning** by the G-BA, the G-BA prepares the main contents of the commission (during the course of scoping, see Section 4.9.1) and gives those entitled to comment the opportunity to do so. Simultaneously to commissioning, in its decision the G-BA discloses whether health services research studies that the G-BA agreed upon with the pharmaceutical company are to be considered.

In parallel the G-BA requests the **submission of the dossier** by the pharmaceutical company. This dossier is considered in the assessment.

The results of the information retrieval and the scientific assessment are presented in the **preliminary report**. In the assessment of content, as a rule medical expertise is involved via external experts and the patient perspective is involved via affected persons and/or patient organizations.

Medical expertise is primarily obtained on the basis of a questionnaire sent to external experts at the beginning of the assessment. The feedback provided by external experts is considered in the assessment. Moreover, if necessary, external experts may be involved to clarify specific questions arising during the course of the assessment. External experts are identified via the Institute's own database for external experts (see Section 2.2.2).

The **patient perspective** is determined on the basis of a questionnaire sent to affected persons and/or patient organizations at the beginning of the assessment. The information provided in this questionnaire (e.g. on relevant outcomes and on important subgroups) is considered in the assessment. Affected persons and/or patient organizations are identified via the relevant organizations named in §140f SGB V.

The **preliminary report** includes the preliminary recommendation to the G-BA. After completion, it is first forwarded to the G-BA, the Foundation's Board of Directors, the Foundation Council, and the Board of Trustees. It is published on the Institute's website soon after it is sent to the G-BA.

The preliminary report is subject to a public hearing. As a matter of principle, the hearing is conducted by means of written comments, which can be submitted within a period of 3 weeks from the time of notification on the Institute's website. Optionally, an oral scientific debate with those submitting comments may be held. This debate serves the potentially necessary clarification of aspects of the written comments. The hearing refers in particular to the results of the retrieval and assessment of information presented in the preliminary report.

The **final report**, which is based upon the preliminary report and contains the assessment of the scientific findings (considering the results of the hearing on the preliminary report), represents the concluding product of the work on the commission. The final report must be forwarded to the G-BA within 3 months after the initiation of the commenting procedure on the preliminary report (see the G-BA's Code of Procedure 5th Chapter §31 [271]). The final report and the documentation of the hearing on the preliminary report are first forwarded to the G-BA, as well as to the Foundation's Board of Directors and Foundation Council, and subsequently forwarded to the Foundation's Board of Trustees. These documents are then published on the Institute's website. 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 G-BA will be sent well-founded information on whether, in the Institute's opinion, a new commission on the topic is necessary (if appropriate, a report update). The G-BA then decides on the commissioning of the Institute. Such an update is conducted according to the general methodological and procedural requirements for the Institute's products.

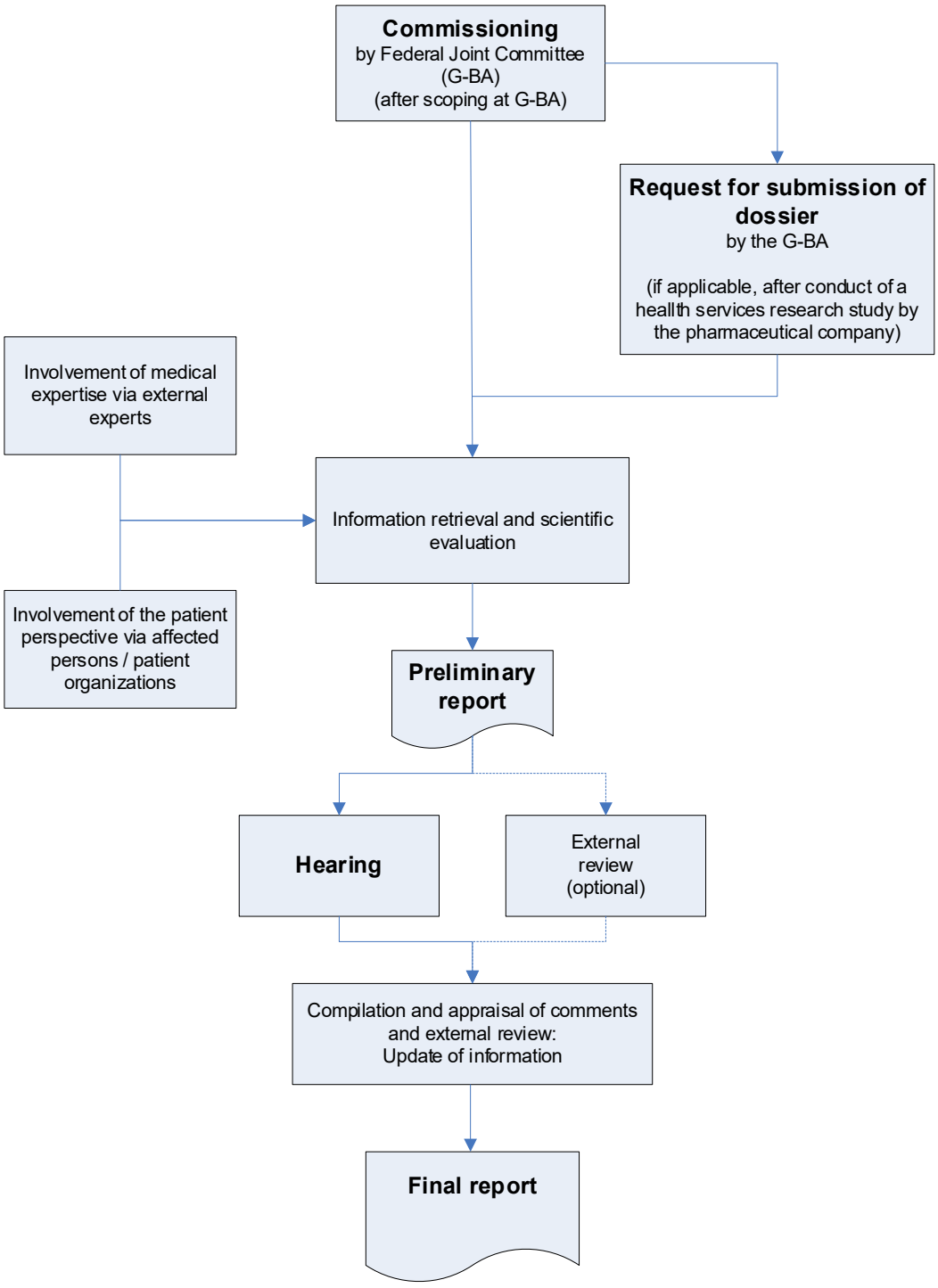


Figure 4: Procedure for the health economic evaluation according to §35b SGB V

2.1.5 Assessment of potential

The procedure for the production of an assessment of the potential of a non-drug intervention is presented in Figure 5. All working steps are performed under the responsibility of the Institute. External experts can be involved in the procedure (see Section 2.2). The internal quality assurance process is not presented in this flowchart.

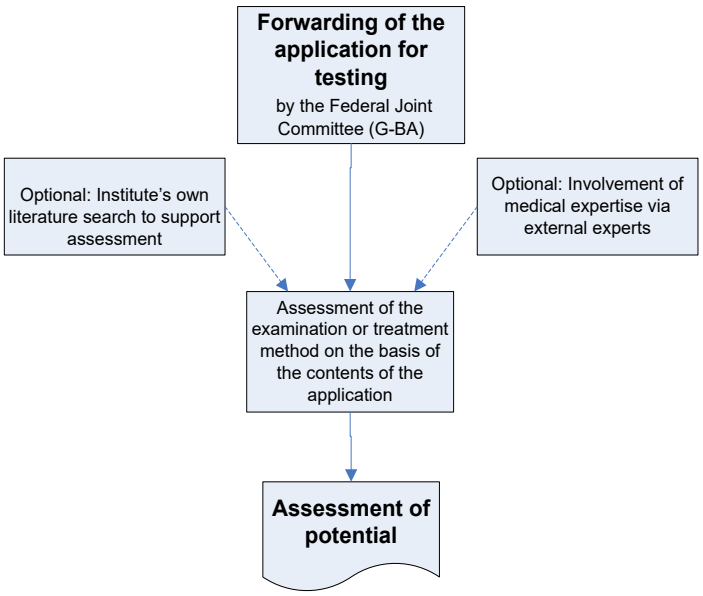


Figure 5: Procedure for the production of an assessment of potential

After the **forwarding of the application for testing** by the G-BA, the assessment of the content of the application is performed under the Institute's responsibility. External medical expertise can be involved for this purpose. This is done in the same way as in dossier assessments, but under consideration of the specific requirements for the protection of the strict confidentiality within the framework of assessments of potential.

The basis of the assessment is the application submitted by the applicant to the G-BA and then forwarded to the Institute. To support the assessment the Institute may optionally conduct its **own literature search**. As the key points of the testing study are an optional part of the application, the Institute may specify these points if the applicant provides no corresponding information.

The process is completed by the preparation of the **assessment of potential**. According to §137e SGB V, within 3 months the G-BA must make a decision on the potential of the examination or treatment method applied for. As a rule, assessments of potential are therefore completed by the Institute within 6 weeks. After completion, the assessment of potential is sent to the G-BA. The assessment is not published as, according to §137e SGB V, the assessment procedure is subject to strict confidentiality. The assessment of potential is only published if the G-BA issues a testing directive during the further course of the procedure.

2.1.6 Assessment according to §137h SGB V

The procedure for the production of an assessment according to §137h SGB V largely corresponds to that of an assessment of potential (Figure 5): The Institute is responsible for all working steps; in this context, external experts may be involved (see Section 2.2.2). However, in contrast to assessments of potential, for assessments according to §137h SGB V, neither the

topic of the assessment nor the main documents are confidential. The internal quality assurance process is not presented in the flow chart.

A hospital submits documents to the G-BA on a new examination or treatment method[12] that is largely based on the use of a high-risk medical device. These documents are made public by the G-BA. After potential supplementation of the documents by further hospitals and affected medical device manufacturers, the G-BA transfers all of the documents providing the basis of the assessment to the Institute.

The Institute conducts an assessment with regard to benefit, harmfulness or ineffectiveness. The basis of the assessment if formed by the documents submitted to the G-BA by a hospital or medical device manufacturer. Optionally, the Institute can conduct its own literature search to support the assessment. External medical expertise can be involved to clarify specific questions. For this purpose, external experts are identified via the Institute's own expert database.

The Institute evaluates whether either a benefit or harmfulness or ineffectiveness can be recognized by means of the documents. As the G-BA is legally obliged to decide on the benefit or harmfulness or ineffectiveness of the method within 3 months, according to §137h SGB V the Institute prepares its assessments within 6 weeks. The respective report is transferred to the contracting agency, the G-BA. The assessment is generally published 4 to 6 weeks after the report was transferred to the G-BA.

2.1.7 Addendum

The procedure for the production of an addendum is presented in Figure 6. All working steps are performed under the responsibility of the Institute, involving the Institute's Scientific Advisory Board where appropriate. The internal quality assurance process is not outlined in this flow chart.

[12] Neue Untersuchungs- oder Behandlungsmethode, NUB

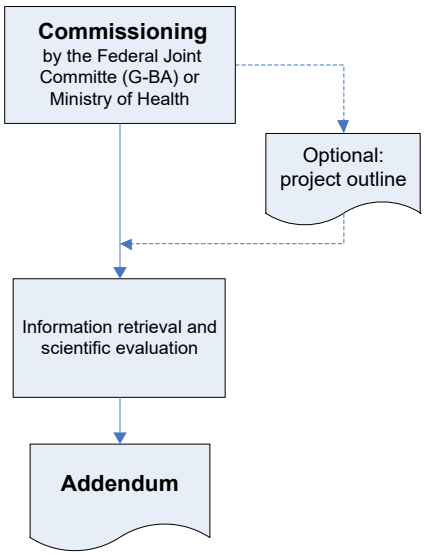


Figure 6: Procedure for the production of an addendum

An addendum can be commissioned if the need for additional work on the commission arises during the consultations on products completed by the Institute. Depending on the type and extent of the research question, it may be meaningful to prepare a **project outline** in which the main steps of the information retrieval and scientific assessment are summarized. The project outline is not published.

In the work on the **addendum**, depending on the type and extent of the research question, it may be meaningful to involve those external experts who were involved in preparing the underlying product of the Institute.

The procedure for publication of an addendum follows that of the original product of the Institute. For example, an addendum on reports is first sent to the contracting agency, as well as to the Foundation Council and the Board of Directors. It is usually forwarded to the Foundation's Board of Trustees 1 week later and published on the Institute's website a further 3 weeks later.

2.1.8 Health information

The Institute produces **health information** for the general public in various formats, which are presented in more detail in Section 7.16.

The production of health information is based on the legal mandate to provide readily understandable information for the general public in accordance with §139a SGB V (see Section 1.1) and the general commission of the G-BA (see Section 1.2).

This information is provided to the public primarily via the website www.gesundheitsinformation.de (and the English-language version www.informedhealth.org).

The website's main focus is on topics related to health and illness. Depending on the breadth and depth of a topic, it may combine several different types of article formats.

The process for the production of health information is presented in Figure 7.

After deciding on the aspects the topic is to cover, the next step is the **systematic information retrieval**, followed by the **scientific evaluation** of the identified publications.

After the **production of the text** and **editorial work**, as a rule, the draft health information is sent out for an **external review** and the draft is then adjusted accordingly, if necessary.

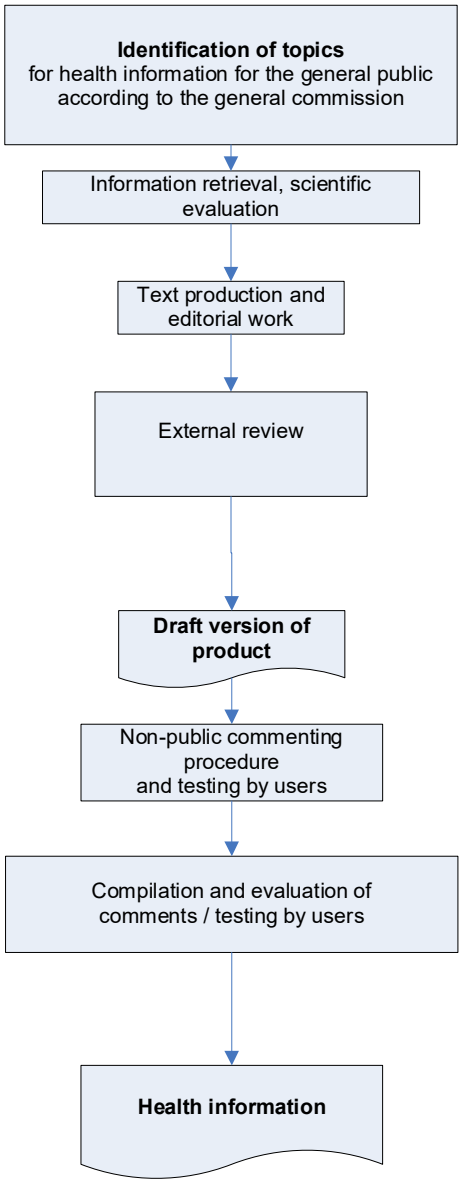


Figure 7: The process for the production of health information

The draft version of a new piece of health information is submitted to those who it was commissioned by, the Board of Trustees, the Foundation's Board of Directors and the

Foundation Council as well as the Scientific Advisory Board for non-public **comments**. Before publication, a health information article undergoes standardised external testing by users – generally at the same time as the commenting procedure. The comments submitted during the 4-week commenting period and the results of the testing by users are summarized and reviewed with regard to any resulting necessary changes to the health information, either content-wise or editorial.

Chapter 7 describes details on the process of topic selection, the information retrieval for the production of health information, the scientific evaluation, and patient involvement.

As a rule, corrections, improvements, and updates of published health information are carried out internally. If extensive or substantial changes to content are made, an external review is performed again. In this case, another non-public commenting procedure and further external testing by users may also follow.

If directly commissioned by the G-BA or the Federal Ministry of Health, the health information is produced in the form of a report, rapid report or addendum. The production and publication of the information follow IQWiG's standard procedure. Usually, the corresponding health information is subsequently published on www.gesundheitsinformation.de / www.informedhealth.org. Where relevant, publication is delayed until the corresponding G-BA guidelines become effective.

A variant of health information is information that can be produced to accompany all other products of the Institute in order to present their results in a way that is readily understandable to the general public. The following adjustments in the production process apply:

- There is no external review by experts, as the relevant expertise was already included in the creation of the IQWiG product. There is a review of the health information in the Institute by the department that created the product.
- In the case of health information on "early" benefit assessments of drugs according to §35a SGB V (dossier assessments and related addenda), no commenting procedure takes place due to the tight deadlines, as stipulated in the Institute's statutes.

2.1.9 Working paper

The procedure for the production of a **working paper** is presented in Figure 8. All working steps are performed under the responsibility of the Institute, involving external experts or the Institute's Scientific Advisory Board, where appropriate. The internal quality assurance process is not presented in this flow chart.

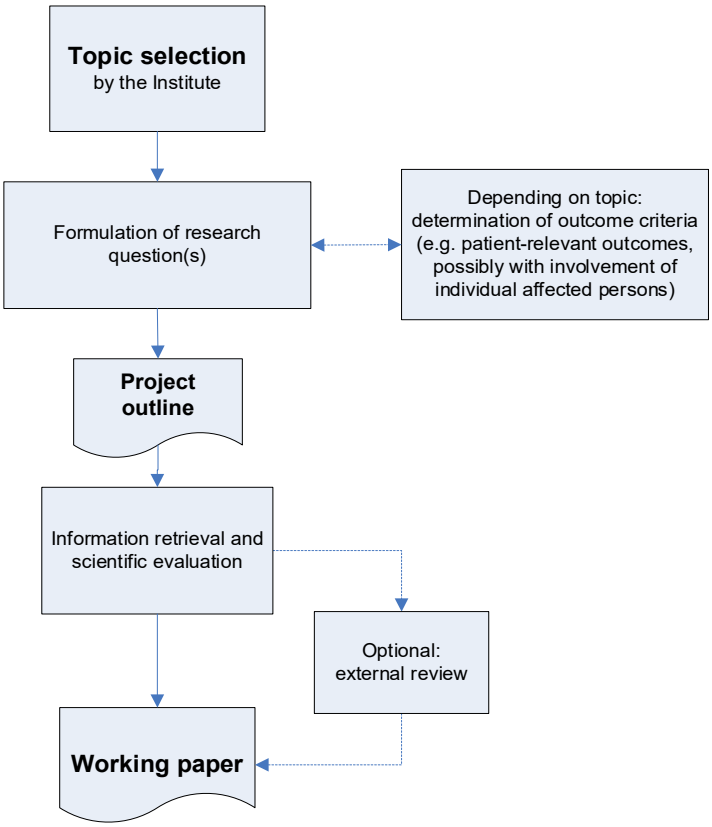


Figure 8: Procedure for the production of a working paper

The production of working papers is conducted (among other things) within the framework of the **general commission** awarded by the G-BA on 21 December 2004. This commission was further specified and adapted in July 2006 and March 2008 with regard to the production of health information. According to the general commission, the Institute was commissioned "by means of documenting and analysing the relevant literature, continuously to study and assess medical developments of fundamental importance and their effects on the quality and efficiency of health care in Germany, and to relay its findings to the G-BA on a regular basis. In this context, the G-BA assumes that, within the framework of the tasks assigned in accordance with §139a (3) SGB V, the Institute will work not only on individual commissions awarded by the G-BA, but will also take on scientific projects on its own responsibility, and relay essential information on relevant health care developments to the G-BA so that it can fulfil its legal obligations. Against the background of this information, the Institute will also develop concrete proposals for individual commissions that it considers relevant."

The need to conduct independent scientific projects therefore results from the Institute's legal remit and the general commission. This also includes projects on the further development of methods, which can also be published as working papers.

The **topic selection** takes place within the Institute, particularly on the basis of the criteria defined in the general commission. The formulation of the research question may take place by

involving patient organizations or seeking the opinion of individual affected patients, especially for the definition of patient-relevant outcomes. The project outline is then prepared.

The **project outline** summarizes the main steps in the information retrieval and scientific assessment. It forms the basis for the preparation of the working paper. The project outline is not published.

The working paper presents the results of the information retrieval and scientific assessments. The quality assurance process can (optionally) include an external review. After completion, the working paper is first sent to the G-BA as well as to the Foundation's Board of Directors and Foundation Council. It is then forwarded to the Foundation's Board of Trustees (usually a week later) and after 3 further weeks published on the IQWiG website. If comments on working papers are received that contain substantial unconsidered evidence, or if the Institute receives such evidence from other sources, the Institute assesses whether it considers it necessary to update the document or not. The general methodological and procedural requirements for the Institute's products apply to such an update.

2.1.10 HTA report

The procedure for the production of HTA reports according to §139b (5) SGB V is shown in Figure 9. The HTA report is prepared by the external experts (see Section 2.2.2) using IQWiG's methods and supplemented by IQWiG with a publisher's comment. The internal quality assurance processes are not included in this flow chart.

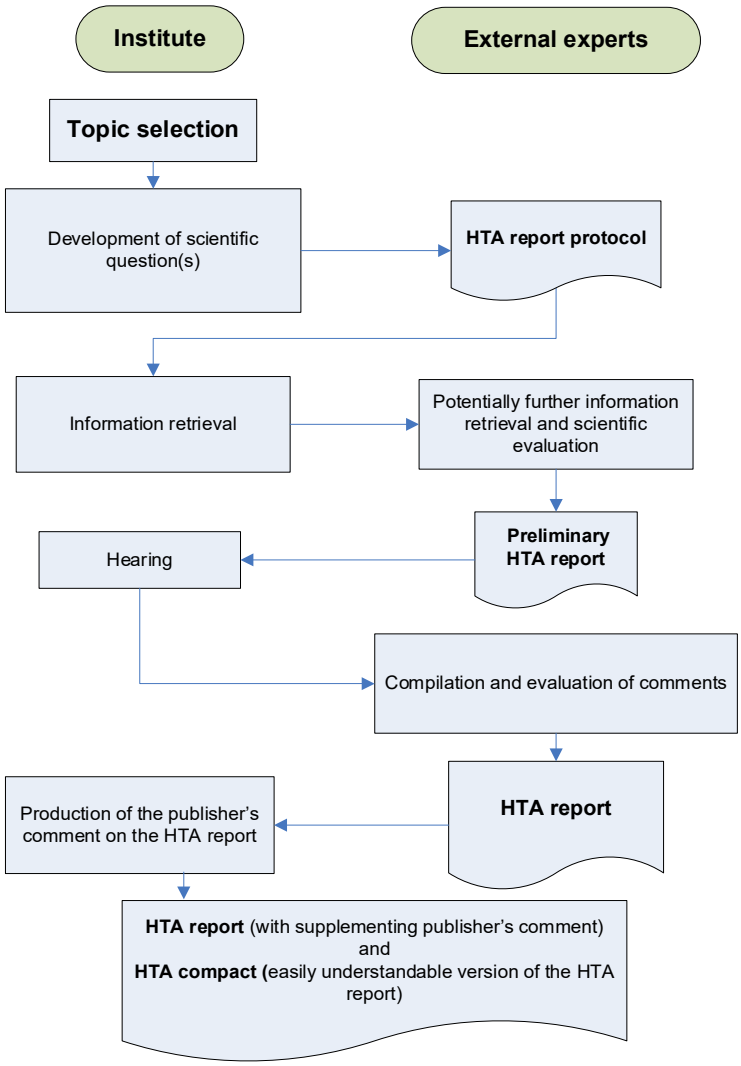


Figure 9: Procedure for the production of an HTA report

After the Institute has completed the topic selection for the HTA reports (see Section 6.3), the scientific HTA question is formulated.

The **HTA report protocol** is prepared by external experts. It contains the precise scientific question including the outcome criteria (e.g. patient-relevant outcomes), the inclusion and exclusion criteria for the information to be used in the assessment, as well as the presentation of the project-specific methods for the retrieval and assessment of this information according to the Institute's methods. It forms the basis of the production of the preliminary HTA report. The HTA report protocol is published on the Institute's website and the Foundation Board, the Foundation Council, the Board of Trustees, the G-BA and the Federal Ministry of Health are informed about the publication.

In the **preliminary HTA report** the external experts present the results of the information retrieval and the scientific assessment, including their own conclusion. After completion, it is also published on the Institute's website and the Foundation Board, the Foundation Council,

the Board of Trustees, the G-BA, and the Federal Ministry of Health are informed about the publication.

The preliminary HTA report is subject to a hearing. The hearing is as a matter of principle conducted by means of written comments, which can be submitted within a period of at least 4 weeks from the time of notification on the Institute's website. Optionally, an oral scientific debate with persons who submitted comments is conducted. If necessary, this debate serves to clarify issues of the written comments. Besides the project-specific methodological approach to answer the research question, the hearing particularly addresses the results of the retrieval and assessment of information presented in the preliminary HTA report. The hearing is administered and conducted by IQWiG. The comments are evaluated and appreciated by the external experts in the HTA report.

Building on the preliminary HTA report, the **HTA report** contains the assessment of scientific findings, under consideration of the results of the hearing on the preliminary HTA report, and represents the final product of the external experts. The HTA report is preceded by a **publisher's comment** in which the Institute classifies the results. In addition, the Institute produces **HTA compact**, an easily understandable summary of the HTA report.

The HTA report, HTA compact, and the documentation of the hearing on the preliminary HTA report are first sent to the Foundation Board, the Foundation Council and the Board of Trustees as well as to the G-BA and the Federal Ministry of Health. These documents are generally published on the Institute's website 2 weeks later.

2.1.11 Evidence reports

The procedure for the production of an evidence report is shown in Figure 10.

Evidence reports are produced as part of a commission by the Federal Ministry of Health to conduct an evidence search for a selected clinical practice guideline and serve guideline groups as an evidence basis for the development of recommendations for action. To this end, the guideline coordinators formulate specific research questions in consultation with patient representatives and after provision of advice by the AWMF, for which IQWiG produces separate evidence reports. The internal quality assurance process is not presented in this flow chart.

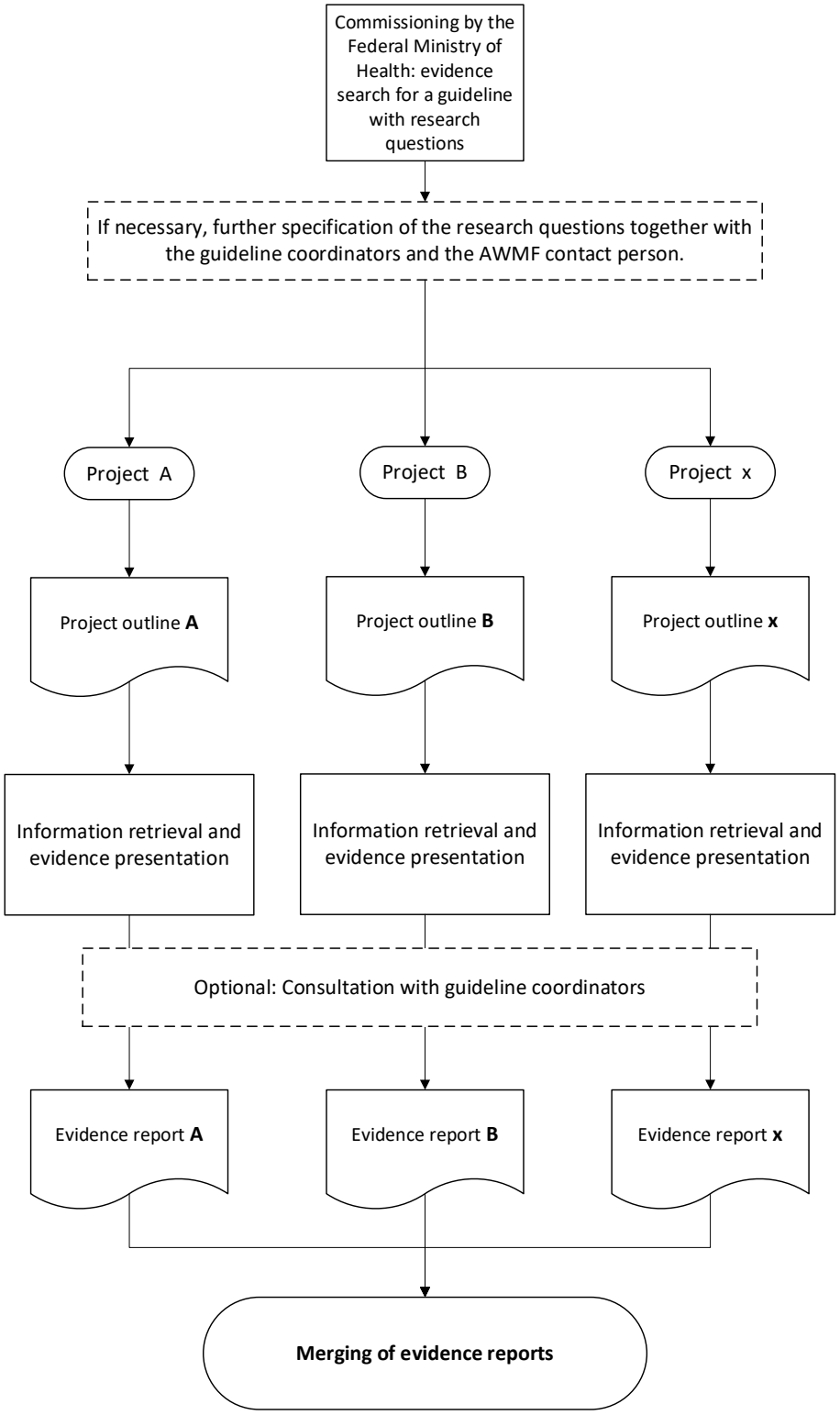


Figure 10: Procedure for the production of evidence reports within an evidence search for a guideline according to §139a SGB V

After commissioning by the Federal Ministry of Health, the research question to be examined per evidence report may be further specified together with the guideline coordinators of the corresponding guideline and the contact person at the AWMF.

The project outline summarizes the essential steps of information retrieval and evidence presentation. It forms the basis for the production of the evidence report. The project outline is not published, but sent for information to the guideline coordinators of the relevant guideline and the contact person at the AWMF.

The information retrieval results and the evidence available are presented in the evidence report. After completion of an evidence report, it is sent to the guideline coordinators of the relevant guideline and the contact person at the AWMF.

After completion of all evidence reports for a commission on an evidence search for a guideline, they are sent together to the Federal Ministry of Health, the Board of Directors of the Foundation, the Foundation Council as well as the AWMF and then (usually 1 week later) to the Board of Trustees. The report is usually published on the Institute's website 4 weeks after it is sent to the contracting agency.

2.2 General aspects in the preparation of products

The following procedures and aspects that are valid for all products are presented in this chapter:

- the involvement of affected persons in the preparation of IQWiG products
- selection of external experts for collaboration in the preparation of products
- guarantee of scientific independence in the preparation of products
- review of products
- the commenting procedure
- publication of products

Moreover, the provision of scientific advice in relation to the preparation of products is described.

2.2.1 Involvement of affected persons in the preparation of IQWiG products

The involvement of affected persons within the preparation of systematic reviews and HTA reports is now an established international standard of benefit assessment [143,234,440]. The involvement of affected persons at IQWiG primarily takes place in the beginning of the work on a project within the framework of the specification of patient-relevant outcomes and relevant subgroups. Moreover, within the framework of the hearing procedure, affected persons have the option of being involved in the preparation of products (see Section 2.2.5). Within the framework of the production of health information, self-help organizations can be questioned

about the need for information of affected persons and about the challenges arising in coping with the disease. The drafts of the health information products regularly undergo external user testing. Moreover, topic-specific experience reports by affected persons are recorded (see Section 7.9).

Affected persons can particularly be patients (if appropriate, represented by their parents or other relatives) as well as potential participants in prevention measures.

In the selection of participants the focus is placed on persons actually affected, as patient representatives or representatives of self-help groups are sometimes not patients themselves and cannot assess in a comparable way how affected persons perceive symptoms, functions and activities, or are impaired in their quality of life.

In order to find affected persons the patient representation in the G-BA is regularly asked to name affected persons for a topic directly or via its member organizations. In addition, the Institute may contact or search for affected persons via national or local self-help organizations or groups, hospitals or medical practices, external experts or other routes.

Two different ways exists for involving affected persons: Firstly, a personal consultation meeting can be held where affected persons and IQWiG employees talk about a disease in a small circle of people. Secondly, the perspectives and experiences of affected persons can be requested in writing. The names of affected persons who participated in the consultation meeting or filled in the questionnaire on the consultation are as a matter of principle not published, unless they explicitly approve that their names are published.

In what form affected persons can be involved in the Institute's work primarily depends on how much time is available for the work on the commission and whether the topic of the commission is confidential. Furthermore, the renewed involvement of affected persons can be dispensed with if a topic of a commission has already been addressed within an earlier consultation.

For all of the Institute's products, Table 2 shows the types of potential involvement of affected persons that go beyond the product-specific commenting procedures. The respective product-specific processes are shown in Section 2.1.

Table 2: The Institute's products and potential types of involvement of affected persons

Institute's product	**Type of involvement of affected persons**
Report Rapid report	Oral consultation
Dossier assessment Health economic evaluation according to §35b SGB V	Written consultation
Assessment of potential Assessment according to §137h SGB V Addendum	No involvement
Health information	Oral consultation, user testings, experience reports
Working paper	Oral or written consultation, as required
HTA report	Oral consultation
Evidence report	Involvement through the respective guideline coordinators
HTA: health technology assessment; SGB V: Sozialgesetzbuch (Social Code Book V – Statutory Health Insurance)	

2.2.2 Selection of external experts

In accordance with its legal remit, the Institute involves external experts in its work. External experts are persons who are awarded research commissions within the framework of the preparation of the Institute's products or their review or who advise the Institute on medical or other topic-related research questions. The Institute awards these commissions following general procurement principles in a transparent and non-discriminating competition.

Announcements for research commissions according to §139b (3) SGB V as well as §139b (5) SGB V are published on the Institute's website. Exceptions are possible, particularly in the case of urgent commissions. Commissions with a volume above the current threshold value of the procurement regulations of the European Union (EU) are advertised throughout the EU. The specific requirements regarding the suitability of applicants are published in the corresponding announcements or tendering documents.

The commissioning of external experts for dossier assessments, HEEs according to §35b SGB V, assessments of potential, assessments according to §137h SGB V, and the production of health information is conducted on the basis of information provided by interested persons in a database for external experts. For inclusion in the database for external experts, the Institute's website offers an access point via which interested experts can enter their profile, including details of their specialty and professional expertise. For the projects to be awarded, in each case the most suitable applicant of the relevant specialty is selected from this expert database by means of a criteria list and then commissioned. Further information on the selection procedure is published on the Institute's website.

2.2.3 Guarantee of professional independence

The scientific and professional independence of the Institute and of the products it is responsible for and publishes have their legal basis in §139a SGB V, as well as in the *Charter* of the Foundation.

A) Guarantee of internal professional independence

The Institute's scientific staff are prohibited from performing external assignments that could in principle query their professional independence. Details are specified in employment contracts and internal regulations.

B) Guarantee of the independence of external experts

Before a contract is signed between the Institute and an external expert or external institution with regard to the preparation of a product, in accordance with §139b SGB V, "all connections to associations and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received" must be disclosed to the Institute.

- Following the usual practice in research to disclose such connections [464,470], within the framework of the selection of external experts, the Institute interprets this regulation as a responsibility to assess these disclosures with regard to the professional independence and impartiality of applicants, or more precisely, whether there are serious doubts about appropriate collaboration due to conflicts of interest. If this is the case, collaboration on the topic of this commission is usually not possible or only possible under specific provisions. As this assessment is performed in relation to a specific commission, collaboration on topics of other commissions is indeed possible. The further process for the selection of external experts is outlined in Section 2.2.2.
- The main basis of the assessment of relationships is self-disclosure using the *Form for disclosure of relationships*, which is published on the Institute's website. Self-disclosure refers to the following types of connections:
  - employment relations/self-employed activities/voluntary activities
  - advisory activities
  - payments, e.g. for presentations, comments, as well as organization and/or participation in conferences and seminars
  - financial support for research activities, other scientific services or patent registrations
  - other financial or other cash-value support (e.g. for equipment, staff or travel expenses, without providing scientific services in return)
  - shares, equity warrants or other shares in a business, patents, registered designs

- other circumstances that, from the perspective of an unbiased observer, could be assessed as a conflict of interest (e.g. activities in health-related interest groups or self-help groups)

The Institute reserves the right to draw upon additional information and verify the completeness and correctness of the reported information.

The names of external experts involved in the preparation of the Institute's products are usually published in these products. As a matter of principle, these publications are freely accessible via the Institute's website. The information on relationships is only published in a summarized form. In this context, for the types of connections covered by the *Form for disclosure of relationships*, it is only stated whether this type of connection existed or not. Specific details, for example, concerning the names of business partners or the amount of any remuneration received, are not published.

2.2.4 Review of the Institute's products

The review of the Institute's products aims in particular at ensuring their high scientific quality. Moreover, other aims may be relevant for individual products, such as comprehensibility for the general public.

All products (including all project-specific publications before conclusion of the commission) are subjected to a comprehensive multi-stage internal quality assurance process. In addition, during the preparation of products, an external review procedure may be performed as an optional further quality assurance step. The choice of internal and external reviewers is primarily made on the basis of their methodological and/or professional expertise.

External reviewers can be identified by a literature search, the expertise of the project group, by contacting scientific societies, or by application during the tendering procedure for work on a commission, etc. In each case, external reviewers must also disclose potential conflicts of interest.

External reviewers are selected by the Institute and their number is not limited. The external reviews are assessed with regard to their relevance for the particular product; they are not published. The names of the external reviewers of final reports and rapid reports are usually published in these documents, including a presentation of their potential conflicts of interests, in analogy to the procedure for external experts.

In addition to the external quality assurance processes described above with the involvement of reviewers selected and commissioned by the Institute, an open and independent reviewing process is guaranteed by the publication of the Institute's products and the associated opportunity to submit comments.

2.2.5 Commenting procedure

A) Organizations entitled to submit comments

In accordance with §139a (5) SGB V, the Institute must ensure that the following parties are given the opportunity to submit comments in all important phases of the assessment procedure: medical, pharmaceutical, and health economic experts (from research and practice), drug manufacturers, relevant organizations representing the interests of patients and self-help groups for the chronically ill and disabled, as well as the Federal Government Commissioner for Patients' Affairs. Their comments must be considered in the assessment. These requirements are taken into account by the fact that hearings are conducted and that the circle of people entitled to submit comments is not restricted. Moreover, all the Institute's products, in accordance with §139a SGB V, are sent to the Board of Trustees before publication. The following parties are represented in the Board of Trustees: patient organizations, the Federal Government Commissioner for Patients' Affairs, organizations of service providers and social partners, as well as the self-government bodies of the supporting organizations of the G-BA.

B) Course of the public commenting procedure (hearings)

The start date and the deadline for submitting comments are announced on the Institute's website. Interested parties can then submit written comments to the Institute. The submission is possible electronically (preferred form) or by post. Optionally, a scientific debate with those submitting comments may additionally be held with the aim of clarifying the content of written comments. On request, employees of the G-BA office can participate in the scientific debate.

In order to avoid inappropriate delays in the Institute's work, the comments must fulfil certain formal requirements. The deadlines are outlined in the respective sections on the product-specific procedures (see Section 2.1). Further information on the commenting procedure, including the conditions for participation in a scientific debate, can be found on the Institute's website.

Comments that fulfil the formal requirements are published in a separate document on the Institute's website (*Documentation of the hearing*). In order to ensure transparency, documents that are submitted together with the comments and are not publicly accessible (e.g. manuscripts) as well as the verbatim meeting minutes of the oral scientific debate – if it took place – are also published.

Within the framework of the hearing there is the option to submit documents of adequate quality of any type that, from the perspective of the respective person submitting comments, are suitable to answer the research question. For example, if a search strategy defined in a report plan is restricted to RCTs, non-RCTs can still be submitted within the framework of the commenting procedure. But in such cases, adequate justification is additionally required of the validity of the causal interpretation of the effects described in such studies.

2.2.6 Publication of the Institute's products

One of the Institute's main tasks is to determine the available evidence on a topic by performing a careful assessment of the information available, and to publish the results of this assessment. It is legally specified that the Institute "must at regular intervals publicly report on its working processes and results, including the bases for decision-making" (§139a (4) SGB V).

To maintain the Institute's independence, it must be ruled out that the contracting agencies or any other interested third parties can exert any influence on the content of the reports. This could lead to conflation of scientific findings with political and/or economic aspects and/or interests. At the same time, it must be avoided that the Institute itself withholds certain findings. All the results obtained by the Institute within the framework of its legal responsibilities are therefore published as soon as possible (with the exception of assessments of potential, see Second Chapter §19 of the G-BA's Code of Procedure [271]). In the case of reports, this also includes the report plan. Product-specific features are noted in those sections in which the procedures are described. In justified exceptional cases, timelines may deviate from the stipulated norm (period between completion and publication of a document).

Unless otherwise agreed, all copyright is held by the Institute.

2.2.7 Scientific advice

In special cases the Institute is involved in the provision of scientific advice to study sponsors, for example within the framework of its collaboration in the European network for Health Technology Assessment (EUnetHTA). In this context the primary goal is to support the design of studies that provide informative data for benefit assessments. In order to ensure the independence of the assessment, including those cases in which a benefit assessment contains studies on which the Institute has provided advice, an appropriate organizational separation of advice and assessment is ensured.

3 Benefit assessment of medical interventions

3.1 Patient-relevant medical benefit and harm

3.1.1 Definition of patient-relevant medical benefit and harm

The term **benefit** refers to positive causal effects, and the term **harm** refers to negative causal effects of a medical intervention on patient-relevant outcomes (see below). In this context, "causal" means that it is sufficiently certain that the observed effects can be ascribed solely to the intervention to be tested [757].

If a comparison is not explicitly named, the terms "benefit" and "harm" refer to a comparison with a placebo (or another type of sham intervention) or no treatment. In the case of a comparison between the medical intervention to be assessed and a clearly defined alternative medical intervention, the following terms are used in the comparative assessment of beneficial or harmful aspects (the terms are always described from the point of view of the intervention to be assessed):

- Beneficial aspects:
  - In the case of an advantage, the term "greater benefit" in comparison with the other intervention is used. Dossier assessments are an exception; in these cases the term "added benefit" is used instead of the term "greater benefit".
  - In the case of a disadvantage, the term "lesser benefit" is used.
  - In the case of comparable effects, the term "comparable benefit" is used.
- Harmful aspects:
  - The terms "greater harm", "comparable harm" and "lesser harm" are used.

The assessment of the evidence should preferably come to a clear conclusion that either there is proof of a(n) (added) benefit or harm of an intervention, or there is proof of a lack of a(n) (added) benefit or harm, or there is no proof of a(n) (added) benefit or harm or the lack thereof, and it is therefore unclear whether the intervention results in a(n) (added) benefit or harm. In addition, in the case of (added) benefit or harm that is not clearly proven, it may be meaningful to perform a further categorization as to whether at least "indications" or even only "hints" of an (added) benefit or harm are available (see Section 3.1.4).

As the benefit of an intervention should be related to patients, this assessment is based on the results of studies investigating the effects of an intervention on patient-relevant outcomes. In this connection, patient-relevant refers to how a patient feels, functions or survives [60]. Consideration is given here to both the intentional and unintentional effects of the intervention that in particular allow an assessment of the impact on the following patient-relevant outcomes to determine the changes related to disease and treatment:

1) mortality
2) morbidity (symptoms and complications)
3) health-related quality of life

These outcomes are also named in SGB V as outcomes primarily to be considered, for example, in §35 (1b) SGB V. As supplementary information, consideration can be given to the time and effort invested in relation to the disease and the intervention. This also applies to patient satisfaction, insofar as health-related aspects are represented here. However, a benefit or added benefit cannot be determined on the basis of these 2 outcomes alone.

For all listed outcomes it may be necessary that an assessment is made in relation to information on how other outcomes are affected by the intervention. In the event of particularly serious or even life-threatening diseases, for example, it is usually not sufficient only to demonstrate an improvement in quality of life by application of the intervention to be assessed, if at the same time it cannot be excluded with sufficient certainty that serious morbidity or even mortality are adversely affected to an extent no longer acceptable. This is in principle consistent with the ruling by the highest German judiciary that certain (beneficial) aspects must be assessed only if therapeutic effectiveness has been sufficiently proven [109]. On the other hand, in many areas (particularly in palliative care) an impact on mortality cannot be adequately assessed without knowledge of accompanying (possibly adverse) effects on quality of life.

In accordance with §35b (1) Sentence 4 SGB V, the following outcomes related to patient benefit are to be given appropriate consideration: increase in life expectancy, improvement in health status and quality of life, as well as reduction in disease duration and adverse effects. These dimensions of benefit are represented by the outcomes listed above; for example, the improvement in health status and the reduction in disease duration are aspects of direct disease-related morbidity; the reduction in adverse effects is an aspect of therapy-related morbidity. Those outcomes reliably and directly representing specific changes in health status are primarily considered. In this context, individual affected persons are especially involved in the topic-related definition of patient-relevant outcomes. In the assessment of quality of life, only instruments should be used that are suited for application in clinical trials and have been evaluated accordingly [225]. In addition, valid surrogate endpoints can be considered in the benefit assessment (see Section 3.1.2).

Both beneficial and harmful aspects can have different relevance for the persons affected; these aspects may become apparent through qualitative surveys or the Institute's consultations with affected persons in connection with the definition of patient-relevant outcomes (examples of corresponding methods are listed at the end of Section 3.1.4). In such a situation it may be meaningful to establish a hierarchy of outcomes. General conclusions on benefit and harm are then primarily based on proof regarding higher-weighted outcomes. Planned subgroup and sensitivity analyses are then primarily conducted for higher-weighted outcomes, whereas such analyses are not routinely conducted for the remaining ones.

Diagnostic tests can be of indirect benefit by being a precondition for therapeutic interventions through which it is possible to achieve an effect on the patient-relevant outcomes mentioned above. The precondition for the benefit of such tests is therefore the existence and the proven benefit of a treatment for patients, depending on the test result.

Interventions can also have consequences for those indirectly affected, for example, relatives and carers. If appropriate, these consequences can also be considered within the framework of the Institute's reports.

The term **benefit assessment** refers to the whole process of the assessment of medical interventions with regard to their positive and negative causal effects compared with a clearly defined alternative treatment, a placebo (or a different type of sham intervention), or no treatment. In this context, beneficial and harmful aspects of an intervention are initially assessed on an outcome-specific basis and then presented. In addition, a combined evaluation of outcome-related beneficial and harmful aspects is possible (see Section 3.1.4) so that, for example, when the effects on all other outcomes have been analysed, the outcome-specific lesser harm from an intervention (in terms of a reduction in adverse effects) can lead to the balanced conclusion of an added benefit.

3.1.2 Surrogates of patient-relevant outcomes

Surrogate endpoints are frequently used in medical research as a substitute for patient-relevant outcomes, mostly to arrive at conclusions on patient-relevant (added) benefits earlier and more simply [21,251,566]. Most surrogate endpoints are, however, unreliable in this regard and can be misleading when used in a benefit assessment [135,289,297]. Surrogate endpoints are therefore normally considered in the Institute's benefit assessments only if they have been validated beforehand by means of appropriate statistical methods within a sufficiently restricted patient population and within comparable interventions (e.g. drugs with a comparable mode of action). A surrogate endpoint can be regarded as valid if the effect of an intervention on the patient-relevant outcome to be substituted is explained to a sufficient degree by the effect on the surrogate endpoint [37,744]. The necessity to evaluate surrogate endpoints may have particular relevance within the framework of the early benefit assessment of drugs (see Section 3.3.3), as regulatory approval procedures primarily investigate the efficacy of a drug, but not always its patient-relevant benefit or added benefit.

There is neither a standard procedure for surrogate endpoint validation nor a general best estimation method nor a generally accepted criterion which, if fulfilled, would demonstrate validity [488]. However, the methodological literature frequently discusses correlation-based procedures for surrogate validation, with estimation of correlation measures at a study level and individual level [378]. The Institute‘s benefit assessments therefore give preference to validations on the basis of such procedures. These procedures usually require a meta-analysis of several randomized studies, in which both the effects on the surrogate endpoint and those on the patient-relevant outcome of interest are investigated [113,510]. Alternative methods [744] are only considered in justified exceptional cases.

For correlation-based procedures the following conditions are normally required to demonstrate validity: on the one hand, a high correlation between the surrogate and the patient-relevant outcome at the individual level, and on the other hand, a high correlation between effects on the surrogate and effects on the patient-relevant outcome at a study level [113,115]. As in the Institute's benefit assessments, conclusions related to groups of patients are drawn, the assessment of the validity of a surrogate endpoint is primarily based on the degree of correlation at the level of treatment effects, i.e. the study level. In addition to the degree of correlation, for the assessment of validity of a surrogate endpoint the reliability of results of the validation process is considered. For this purpose, various criteria are drawn upon [378]. For example, associations observed between a surrogate endpoint and the corresponding patient-relevant outcome for an intervention with a specific mode of action are not necessarily applicable to other interventions used to treat the same disease, but with a different mode of action [249,289,297,488]. The studies on which the validation was based must therefore have been conducted with patient populations and interventions that allow conclusions on the therapeutic indication investigated in the benefit assessment as well as on the test intervention and comparator intervention. In order to assess transferability, in validation studies including various disease entities or interventions, analyses on heterogeneity should at least be available.

In the event that a surrogate endpoint cannot be validated conclusively (e.g. if correlation is not high enough), it is also possible to apply the "surrogate threshold effect (STE) concept" [112,378]. For this purpose, the effect on the surrogate resulting from the studies included in the benefit assessment is related to the STE [115,510].

For the Institute's benefit assessments, conclusions on patient-relevant outcomes can be drawn from the effects on the surrogate, depending on verification of the validity of the surrogate or the evaluation of the STE. The decisive factor for the first point is the degree of correlation of the effects on the surrogate and the patient-relevant outcome and the reliability of validation in the validation studies. In the evaluation of an STE, the decisive criterion is the size of the effect on the surrogate in the studies included in the benefit assessment compared with the STE. In the case of a statistically significant effect on the surrogate endpoints, all gradations of conclusions on the (added) benefit with regard to the corresponding patient-relevant outcome according to Section 3.1.4 are possible, depending on the constellation.

Surrogate endpoints that are not valid or for which no adequate validation procedure was conducted can nevertheless be presented in the Institute's reports. However, independent of the observed effects, such endpoints are not suited to provide proof of verification of an (added) benefit of an intervention.

Depending on the proximity to a corresponding patient-relevant outcome, the literature uses various other terms to describe surrogate endpoints (e.g. intermediate endpoint). However, we dispense with such a distinction here, as the issue of the necessary validity remains unaffected by this. In addition it should be considered that an endpoint can represent a patient-relevant

outcome and, beyond this, can also be regarded as a surrogate (i.e. a substitute) for a different patient-relevant outcome.

3.1.3 Assessment of the harm of medical interventions

The use of any type of medical intervention (drug, non-drug, surgical, diagnostic, preventive, etc.) carries per se the risk of adverse effects. In this context, the term "adverse effects" refers to all effects representing individually perceived or objectively detectable physical or mental harm that may to a greater or lesser extent cause a short- or long-term reduction in life expectancy, an increase in morbidity, or impairment in quality of life. It should be noted that if the term "adverse effects" is used, a causal relationship to the intervention is assumed, whereas the issue of causality still remains open with the term "adverse events" [142].

The term "harm" describes the occurrence of adverse effects when using a medical intervention. The description of harm is an essential and equal component in the benefit assessment of an intervention. It ensures the informed, population-related, but also individual weighing of benefit and harm [770]. A prerequisite for this is that the effect sizes of a medical intervention can be described by means of the data available, both for its desired as well as its adverse effects, and compared with therapy alternatives, for example.

However, in a systematic review, the analysis, assessment, and reporting of the harm of a medical intervention are often far more difficult than those of the (added) benefit. This applies in particular to unexpected adverse effects [142]. Studies are typically designed to measure the effect of a medical intervention on a few predefined outcomes. In most cases, these are outcomes representing effectiveness, while adverse effects are concomitantly recorded as adverse events. The results for adverse events depend heavily on the underlying methods for data collection. For example, explicit queries on defined adverse events normally result in the determination of higher event rates than do general queries [56,390]. To detect unexpected adverse events in particular, general queries about the well-being of patients are however required. In addition, studies designed to specifically detect rare, serious adverse events (including the description of a causal relationship to the medical intervention) are considerably underrepresented in medical research [65,210,389]. Moreover, reporting of adverse events in individual studies is of poor quality, which has also led to amendment of the CONSORT[13] statement for RCTs [388]. Finally, the systematic assessment of the adverse effects of an intervention is also made more difficult by the fact that the corresponding coding in bibliographic databases is insufficient, so that the specific search for relevant scientific literature often produces an incomplete picture [163].

The obstacles noted above often make the investigation of harm more difficult. In cases where complete clinical study reports are available for the assessment, at least sufficient data transparency is also given for adverse events. In addition, especially for drugs, the data are

[13] Consolidated Standards of Reporting Trials

recorded using MedDRA[14] in accordance with a standardized coding system. However, it is still necessary to find a meaningful balance between the completeness of the evaluation of aspects of harm and the resources invested. Consequently, it is necessary to limit the evaluation and reporting to relevant adverse effects. In particular, those adverse effects can be defined as relevant that may

- completely or almost completely offset the benefit of an intervention
- substantially vary between 2 or more otherwise equivalent treatment options
- occur predominantly with treatment options that may be particularly effective
- have a dose-effect relationship
- be regarded by patients as especially important
- be accompanied by serious morbidity or even increased mortality, or be associated with substantial impairment in quality of life

Evaluating and reporting aspects of harm in benefit assessments

The Institute thus observes the following principles when evaluating and reporting adverse effects: In the benefit assessment, the initial aim is to compile a selection of potentially relevant adverse effects that are essential in deciding for or against the use of the intervention to be assessed. In this context, the selection of adverse effects and events is made in accordance with the criteria outlined above.

- As a matter of principle, the overall rates of serious adverse events are used and severe adverse events, if applicable (e.g. those with CTCAE[15] Grade ≥ 3) as well as discontinuations due to adverse events.
- In addition, potentially relevant specific adverse effects are selected for the assessment. This is done in 2 different ways:
  - On the one hand, those specific adverse effects are selected that are of particular importance for the clinical picture or the interventions used in the study or studies. For benefit assessments according to §139a SGB V, this is the primary way of identifying such adverse effects. In this case, the compilation is conducted within the framework of the preliminary search on the respective research question and by involving patients and other people affected.
  - On the other hand, specific adverse effects relevant to the benefit assessment are identified based on the adverse events that occurred in the relevant study or studies. This path is particularly important for benefit assessments of drugs according to §35a SGB V (see Section 3.3.3). Firstly, due to the procedure, no preliminary searches are conducted and secondly, new drugs are as a rule assessed, so that the identification

[14] Medical Dictionary for Regulatory Activities

[15] Common Terminology Criteria for Adverse Events

of unknown or unexpected adverse effects is of greater importance here. In this case, the selection is based on the adverse events, serious adverse events and severe adverse events (if applicable) that are submitted in the dossier by the pharmaceutical company in accordance with the requirements of the G-BA's Rules of Procedure [270]. The criteria for the selection are the relevance of the events to patients and the differences between the treatment arms. For non-serious or non-severe adverse events, additional requirements on the minimum frequency of events may also be specified, provided that this does not influence the overall weighing of benefits and harms to determine the added benefit.

For the specific adverse events selected, in each case the most appropriate operationalization with regard to the certainty of measurements and results is applied. For example, it may be the case that a particular adverse effect is better captured by a Standardized MedDRA Query (SMQ) or by an outcome operationalized outside MedDRA than by a single Preferred Term (PT). It is also checked whether the events selected are consistent with the same content construct. For example, results can be considered inconsistent if a PT (e.g. nasopharyngitis) shows an advantage of the intervention, but a disadvantage in a similar PT (e.g. rhinitis). If no suitable operationalization is available or if the results are inconsistent, they are not usually used to draw conclusions on the harm of an intervention.

3.1.4 Outcome-related assessment

The benefit assessment and the estimation of the extent of the (un)certainty of results generally follow international EBM standards as developed, for example, by the GRADE[16] group [28].

Medical interventions are compared with other interventions, sham interventions (e.g. placebo), or no intervention in respect of their effects on defined patient-relevant outcomes, and their (added) benefit and harm are described in summary. For this purpose, on the basis of the analysis of the scientific data available, for each predefined patient-relevant outcome separately a conclusion on the evidence base of the (added) benefit and harm is drawn in 4 levels with regard to the respective certainty of the conclusion: The data provide either "proof" (highest certainty of conclusions), an "indication" (medium certainty of conclusions), a "hint" (weakest certainty of conclusions) in respect of the benefit or harm of an intervention, or none of these 3 situations applies. The latter is the case if no data are available or the data available do not allow any of the other 3 conclusions to be drawn.

Depending on the research question, the conclusions refer to the presence or lack of a(n) (added) benefit or harm. The prerequisite for conclusions on the lack of a(n) (added) benefit or harm are well-founded definitions of irrelevance ranges (see Section 9.3.5).

[16] Grading of Recommendations, Assessment, Development and Evaluation

A) Certainty of study results

The certainty of results is an important criterion for the inference of conclusions on the evidence base. In principle, every result from an empirical study or systematic review of empirical studies is potentially uncertain and therefore the certainty of results must be examined. In this context, one distinguishes between qualitative and quantitative certainty of results. The qualitative certainty of results is impaired by systematic errors (bias; see Section 9.3.13) such as information errors, selection errors and confounding. The quantitative certainty of results is influenced by random errors caused by sampling (statistical uncertainty).

The qualitative certainty of results is thus determined by the study design, from which evidence levels can be inferred (see Section 9.1.3). It is also determined by (outcome-related) measures for further prevention or minimization of potential bias, which must be assessed depending on the study design (see Section 9.1.4). Such measures include, for example, the blinded assessment of outcomes, an analysis based on all included patients (potentially supported by the application of adequate imputation methods for missing values), and, if appropriate, the use of valid measurement instruments.

The quantitative certainty of results is directly connected to the sample size (i.e. the number of patients investigated in a study or the number of [primary] studies included in a systematic review), as well as to the variability observed within and between studies. If the underlying data allow for this, the statistical uncertainty can be quantified and assessed as the standard error or confidence interval of parameter estimates (precision of the estimate).

The Institute uses the following 3 categories to grade the degree of qualitative certainty at the individual study level and outcome level:

- **high qualitative certainty of results:** results on an outcome from a randomized study with a low risk of bias
- **moderate qualitative certainty of results:** results on an outcome from a randomized study with a high risk of bias
- **low qualitative certainty of results:** results on an outcome from a non-randomized comparative study

B) Inference of the evidence base and certainty of conclusions

In the inference of the evidence base for an outcome, the number of available studies, their qualitative certainties of results, as well as the effects found in the studies are of crucial importance. If at least 2 studies are available, it is first examined whether within a meta-analysis (see Section 9.3.7) a common effect estimate can be meaningfully formed. In this case, the common effect estimate must be statistically significant to infer a proof, an indication or a hint according to the existing certainty of results.

There are situations in which a common effect estimate is not meaningful (see Section 9.3.7). On the one hand, the study results can be too heterogeneous. On the other hand, homogeneous results from a few studies can also lead to common effect estimates that are not informative or very imprecise for models with random effects [49,631]. In such situations, the results are summarized qualitatively or (particularly in the case of heterogeneous results with more than 4 studies) the prediction interval is used. If the qualitative summary or the position of the prediction interval allow a conclusion in the sense of the research question, conclusive effects are present. Conclusive effects are understood to mean a data situation in which it is possible to infer an effect in the sense of the research question, even though a common estimate of the effect is not meaningfully possible. Here, a distinction is made between moderately conclusive and clearly conclusive effects (see below). If the present data situation allows no conclusion in the sense of the research question, the effects are not conclusive.

The following situations lead to conclusive effects:

- Conclusive effects are present if the prediction interval for displaying heterogeneity in a meta-analysis with random effects (see Section 9.3.7) is presented and does not cover the zero effect.
- If the prediction interval is not presented or it covers the zero effect, unidirectional effects are present in the following situation. The effect estimates of 2 or more studies are conclusive and for these studies, all of the following conditions apply:
  - The overall weight of these studies is 80% or greater.
  - At least 2 of these studies show statistically significant results.
  - At least 50% of the weight of these studies is based on statistically significant results.

    In this context, the weights of these studies generally come from a meta-analysis with random effects (see Section 9.3.7).

If conclusive effects are moderately or clearly conclusive, if possible, a decision is made on the basis of the location of the prediction interval. As the prediction interval is generally only presented if at least 4 studies are available (see Section 9.3.7), the classification into effects that are moderately or clearly conclusive depends on the number of studies.

- **2 studies:** conclusive effects are always clearly conclusive.
- **3 studies:**
  - All studies show statistically significant results. The conclusive effects are clearly conclusive.
  - Not all of the 3 studies show statistically significant results. The conclusive effects are moderately conclusive.
- **4 or more studies:**

- All studies show statistically significant results in the same direction of effects: The conclusive effects are clearly conclusive.
- The prediction interval does not cover the zero effect: The conclusive effects are clearly conclusive.
- The prediction interval covers the zero effect: The conclusive effects are moderately conclusive.

In the case of heterogeneous situations, moderately and clearly conclusive effects correspond to moderately and clearly unidirectional effects, respectively. In homogeneous situations, the use of the unidirectionality concept is not meaningful, so that the term "conclusive effects" must be used here to describe that a data situation is present in which a conclusion in the sense of the research question is possible without a quantitative summary of the study results.

Impact of the certainty of results and further factors

For the case that the available studies show the same qualitative certainty of results or only one study is available, with these definitions the regular requirements for the evidence base to infer conclusions with different certainties of conclusions can be specified. As described above, the Institute distinguishes between 3 different certainties of conclusions: proof, indication and hint.

A conclusion on proof generally requires that a meta-analysis of studies with a high qualitative certainty of results shows a corresponding statistically significant effect. If a meta-analysis cannot be conducted, at least 2 studies conducted independently of each other and showing a high qualitative certainty of results and a statistically significant effect should be present, the results of which are not called into question by further comparable studies with a high certainty of results (consistency of results). These 2 studies do not need to have an exactly identical design. Which deviations in design between studies are still acceptable depends on the research question. Accordingly, a meta-analysis of studies with a moderate qualitative certainty of results or a single study with a high qualitative certainty of results can generally provide only an indication, despite statistically significant effects.

On the basis of only one study, in exceptional cases proof can be inferred for a specific (sub)population with regard to an outcome. This requires the availability of a clinical study report according to the ICH[17] guidelines [385] and the fulfilment of the other requirements stipulated for proof. In addition, the study must fulfil the following specific requirements:

- The study is a multi-centre study, at least 1000 patients were included in each study arm and there are at least 10 centres. The number of 1000 patients as well as the number of 10 centres serve as orientation for the Institute and do not mean rigid limits.
- The effect estimate observed has a very small corresponding p-value ($p < 0.001$).

[17] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

- The result is consistent within the study. For the (sub)population of interest, analyses of different further subpopulations are available (particularly subpopulations of study centres), which in each case provide evaluable and sufficiently homogeneous effect estimates. This assessment of consistency is only possible for binary data if a certain minimum number of events has occurred.
- The analyses for the subpopulations addressed above are available for all relevant outcomes, i.e. these analyses are not restricted to individual selected outcomes

It is possible that in the case of the existence of only one study, which alone provides only an indication or a hint, the evidence base may be changed by additional indirect comparisons. However, high methodological demands must be placed on indirect comparisons (see Section 9.3.8). In addition, in the case of a homogeneous data situation, it is possible that by adding indirect comparisons the precision of the effect estimate increases, which plays an important role when determining the extent of added benefit (see Section 3.3.3).

A meta-analysis of studies with a low qualitative certainty of results or an individual study with a moderate qualitative certainty of results (both with a statistically significant effect) generally only provides a hint.

An overview of the regular operationalization is shown in Table 3. In justified cases further factors influence these evaluations. The assessment of surrogate endpoints (see Section 3.1.2), the presence of serious deficiencies in study design or justified doubts about the transferability to the treatment situations in Germany may, for example, lead to a reduction in the certainty of conclusions. On the other hand, great effects or a clear direction of an existing risk of bias, for example, can justify an increase in certainty.

Table 3: Certainty of conclusions regularly inferred for different evidence situations if studies with the same qualitative certainty of results are available

		Number of studies				
		1 (with statistically significant effect)	≥ 2			
			Common effect estimate meaningful	Common effect estimate not meaningful		
			Meta-analysis statistically significant	Conclusive effects[a]		
				Clear	Moderate	No
Qualitative certainty of results	High	Indication	Proof	Proof	Indication	–
	Moderate	Hint	Indication	Indication	Hint	–
	Low	–	Hint	Hint	–	–
a. See text in Section 3.1.4 B for explanation of term.						

If several studies with a different qualitative certainty of results are available, then first only the studies with the higher-quality certainty of results are examined, and conclusions on the

evidence base are inferred on this basis according to Table 3. In the inference of conclusions on the evidence base for the whole study pool the following principles then apply:

- The conclusions on the evidence base, when restricted to higher-quality studies, are not weakened by the addition of the other studies, but at best upgraded.
- The confirmation (replication) of a statistically significant result of a study with a high qualitative certainty of results, which is required to infer proof, can be provided by one or more results of moderate (but not low) qualitative certainty of results within the framework of a conjoint meta-analysis. In this context the weight of the study with a high qualitative certainty of results should have an appropriate size (between 25 and 75%).
- If the meta-analytical result for the higher-quality studies is not statistically significant or if no conclusive effects are shown in these studies, then conclusions on the evidence base are to be inferred on the basis of results of the whole study pool, whereby the certainty of conclusions is determined by the lowest qualitative certainty of results of all studies included.

According to these definitions and principles, a corresponding conclusion on benefit is inferred for each outcome separately. Considerations on the assessment across outcomes are presented in the following section (see Section 3.1.5).

3.1.5 Summarizing assessment

These conclusions, drawn separately for each patient-relevant outcome within the framework of the deduction of conclusions on the evidence base, are then summarized (as far as possible) in one evaluating conclusion in the form of a weighing of benefits and harms. If proof of a(n) (added) benefit and/or harm exists with regard to Outcomes 1 to 3 of Section 3.1.1, the Institute presents (insofar as is possible on the basis of the data available)

1) the benefit
2) the harm
3) (if appropriate) the weighing of benefit and harm

In this context, characteristics related to age, gender, and personal circumstances are considered.

One option in the conjoint evaluation of benefit and harm is to compare the outcome-related beneficial and harmful aspects of an intervention. In this context, the effects on all outcomes (qualitative or semi-quantitative as in the early benefit assessment according to §35a SGB V) are weighed against each other, with the aim of drawing a conclusion across outcomes with regard to the benefit or added benefit of an intervention. A further option in the conjoint evaluation is to aggregate the various patient-relevant outcomes into a single measure or to reach an overall conclusion by weighting them. The conjoint evaluation of benefit and harm is specified depending on the topic of interest (see also Section 4.3.3).

3.2 Special aspects of the benefit assessment

3.2.1 Impact of unpublished study results on conclusions

An essential prerequisite for the validity of a benefit assessment is the complete availability of the results of the studies conducted on a topic. An assessment based on incomplete data or possibly even selectively compiled data may produce biased results [233,377] (see also Section 9.3.13). The bias in published evidence through publication bias and outcome reporting bias has been described comprehensively in the literature [204,501,668,721]. In order to minimize the consequences of such bias, beyond a search in bibliographic databases, the Institute conducts additional searches in trial registries and sends requests to third parties concerning the transfer of data, especially to manufacturers (see also Sections 8.1.2 and 8.1.3).

This transfer of otherwise unpublished information by manufacturers can only solve the problem of bias caused by unpublished evidence if the transfer is itself not selective but complete. An incomplete transfer of data carries a risk of bias for the result of the benefit assessment. This risk must be considered in the conclusions of a benefit assessment.

Table 4 below describes what constellations carry a risk of bias for assessment results, and what consequences arise for the conclusions of a benefit assessment. Scenarios 1 to 4 refer to benefit assessments with requests to third parties concerning the transfer of data (e.g. requests to manufacturers); Scenarios 5 to 7 to those without a request concerning the transfer of data.

Benefit assessments with transfer of data by third parties

If in a benefit assessment with a transfer of data by third parties, this transfer was complete and no evidence is available that further data are missing to a more than negligible extent (Scenario 1), bias is classified as improbable. The conclusions drawn from the assessment of the data are therefore adopted without limitation in the conclusions of the benefit assessment.

Table 4: Scenarios for data completeness and consequences for the conclusions of a benefit assessment

Scenario	Data transfer by third parties (e.g. manufacturer data)	Evidence that data are missing overall	Bias through publication bias	Assessment / Impact on the conclusions
1	Complete	No or to a negligible extent	Improbable	No limitation of the conclusions
2	Complete	Yes, to a moderate extent	Possible	Limitation of the certainty of conclusions[a]
3	Complete	Yes, to a major extent	Probable	No proof (and no indication or hint) of benefit or harm
4	Incomplete	Yes or unclear[b]	Probable or possible	No proof (and no indication or hint) of benefit or harm
Benefit assessments without requests to third parties concerning the transfer of data				
5	No transfer of data planned	No or to a negligible extent	Improbable	No limitation of the conclusions
6	No transfer of data planned	Yes, to a moderate extent	Possible	Limitation of the certainty of conclusions[a]
7	No transfer of data planned	Yes, to a major extent	Possible	No proof (and no indication or hint) of benefit or harm

a. In the case of benefit assessments where the Institute conducts its own commenting procedure, the conclusions of the assessment may also be subject to reservations.
b. If, in exceptional cases, the party transferring data proves that the amount of missing data is certainly irrelevant, the conclusions are not limited.

If, in the case of a complete transfer of data by the manufacturer approached, other searches prove that data are missing to a moderate or major extent (e.g. from investigator-initiated trials [IITs] or trials by other manufacturers) to which the manufacturer does not have access, there is no selective transfer of data by the manufacturer. However, bias due to the other data missing elsewhere is possible depending on the extent of missing data (Scenario 2) or even probable (Scenario 3). In the conclusions of the benefit assessment, the certainty of a conclusion on benefit (in terms of proof, indication or hint of benefit or harm) is therefore weakened accordingly or not inferred at all.

If the transfer of data is incomplete (Scenario 4), a selective transfer of data is assumed. Other relevant unpublished data that are not accessible through the steps of the literature search may exist. Further analysis of the limited data available and any conclusions inferred from them with regard to benefit or harm are probably seriously biased in this situation and therefore do not form a valid basis of assessment. Consequently, no proof (nor indication nor hint) of a benefit or harm of the intervention to be assessed can be determined in this situation, independently of the results observed in the (selectively) presented data.

Benefit assessments without transfer of data by third parties

If, in a benefit assessment without planned transfer of data by third parties, missing data are not identified (Scenario 5), there are no limitations to the conclusions of the benefit assessment.

However, if missing data are identified (e.g. by comparing registered and published studies), bias due to publication bias is possible (Scenario 6) or even probable (Scenario 7). The distinction between the two scenarios is based on the estimated proportion of missing data. If Scenario 6 applies (publication bias possible), the certainty of conclusions is downgraded. Alternatively, the conclusions can be made subject to reservations if, in the course of a commenting procedure conducted by IQWiG on a benefit assessment, there is a possibility that missing data will be subsequently supplied. If Scenario 7 applies (publication bias likely), no proof (and no indication or hint) of a benefit or harm is inferred. In this case, only the available and missing information is presented.

In certain cases (e.g. depending on the data transfer procedure and data proportion, division of the benefit assessment into research sub-questions) it may be possible, despite evidence of missing data, to reduce the extent of publication bias by assessing a demonstrably unbiased sub-pool of studies. However, if studies from different manufacturers are available on a particular research question, the restriction to the data of a single manufacturer may not be appropriate [343].

3.2.2 Dramatic effect

If the course of a disease is certainly or almost certainly predictable, and no treatment options are available to influence this course, then the benefit of a medical intervention can also be inferred from the observation of a reversal of the (more or less) deterministic course of the disease in well-documented case series of patients. If, for example, it is known that it is highly probable that a disease leads to death within a short time after diagnosis, and it is described in a case series that, after application of a specific intervention, most of those affected survive for a longer period of time, then this “dramatic effect” may be sufficient to infer a benefit. An example of such an effect is the substitution of vital hormones in diseases with a failure of hormone production (e.g. insulin therapy in patients with diabetes mellitus type 1). An essential prerequisite for classification as a “dramatic effect” is sufficiently reliable documentation of the fateful course of the disease in the literature and of its diagnosis in the patients included in the study to be assessed. In this context, possible harms of the intervention should also be taken into account. Glasziou et al. [279] have attempted to operationalize the classification of an intervention as a “dramatic effect”. In a first approach they propose to regard an observed effect as not explicable solely by the impact of confounding factors if it was significant at a level of 1% and, expressed as the relative risk, exceeded the value of 10 [279]. This magnitude serves as orientation for the Institute and does not represent a rigid threshold. Glasziou et al. [279] made their recommendation on the basis of results of simulation studies, according to which an observed relative risk of 5 to 10 can no longer be plausibly explained only by confounding factors. This illustrates that a corresponding threshold also depends on the attendant

circumstances (among other things, the quality of studies used to determine the existence of a dramatic effect or consistent results on an outcome category). This dependence is also reflected in the recommendations of other working groups (e.g. the GRADE group) [307].

If, in the run-up to the work on a specific research question, sufficient information is available indicating that a dramatic effect caused by the intervention to be assessed can be expected (e.g. because of a preliminary literature search), then information retrieval will also include a search for studies that show a higher uncertainty of results due to their design.

3.2.3 Study duration

Study duration is an essential criterion in the selection of studies relevant to the benefit assessment. In the assessment of a therapeutic intervention for acute diseases where the primary objective is, for example, to shorten disease duration and alleviate acute symptoms, it is not usually meaningful to call for long-term studies, unless late complications are to be expected. On the other hand, in the assessment of therapeutic interventions for chronic diseases, short-term studies are not usually suitable to achieve a complete benefit assessment of the intervention. This especially applies if treatment is required for several years, or even lifelong. In such cases, studies covering a treatment period of several years are particularly meaningful and desirable. As both benefits and harms can be distributed differently over time, in long-term interventions the meaningful comparison of the benefits and harms of an intervention is only feasible with sufficient certainty if studies of sufficient duration are available. However, individual aspects of the benefits and harms may quite well be investigated in short-term studies.

With regard to the selection criterion of minimum study duration, the Institute primarily follows standards for demonstrating the effectiveness of an intervention. In the assessment of drugs, the Institute will in particular resort to information provided in guidelines specific to therapeutic indications, which are published by regulatory authorities (e.g. [227]). As the benefit assessment of an intervention also includes aspects of harm, the generally accepted standards in this respect are also relevant when determining the minimum study duration. Moreover, for long-term interventions as described above, the Institute will resort to the relevant guidelines for the criterion of long-term treatment [370]. In individual cases, the Institute may deviate from this approach (and will justify this deviation), for example, if a topic requires longer follow-up, or if specific (sub)questions apply to a shorter period. Such deviations may also be indicated if short-term effects are a subject of the assessment (e.g. in the assessment of newly available/approved interventions and/or technologies where no appropriate treatment alternative exists).

3.2.4 Patient-reported outcomes

The patient-relevant dimensions of benefit outlined in Section 3.1.1 can also include patient-reported outcomes (PROs). In addition to health-related quality of life, PROs can also cover other dimensions of benefit, for example, disease symptoms. As in the assessment of quality of

life, instruments are required that are suitable for use in clinical trials [225,719]. In the selection of evidence (especially of study types) to be considered for the demonstration of an effect, the same principles as with other outcomes usually apply [719]. This means that also for PROs (including health-related quality of life, symptoms, and treatment satisfaction), RCTs are best suited to demonstrate an effect.

As information on PROs is subjective due to their nature, open (i.e. non-blinded) studies in this area are of limited validity. The size of the effect observed is an important decision criterion for the question as to whether an indication of a benefit of an intervention with regard to PROs can be inferred from open studies. Empirical evidence shows a high risk of bias for subjective outcomes in open studies [766]. This should be considered in their interpretation (see Section 9.1.4). However, situations are conceivable where blinding of physicians and patients is not possible. In such situations, if possible, other efforts are required to minimize and assess bias (e.g. blinded documentation and assessment of outcomes). Further aspects on the quality assessment of studies investigating PROs are outlined in a US Food and Drug Administration (FDA) guideline [719].

3.2.5 Benefits and harms in small populations

In small populations (e.g. patients with rare diseases or special subgroups of patients with common diseases), there is no convincing argument to deviate in principle from the hierarchy of evidence levels. In this connection, it is problematical that no international standard definition exists as to what is to be understood under a “rare” disease [760]. Independent of this, patients with rare diseases also have the right to the most reliable information possible on treatment options [219]. Non-randomized studies require larger sample sizes than randomized ones because of the need of adjustment for confounding factors. However, due to the rarity of a disease it may sometimes be impossible to include enough patients to provide the study with sufficient statistical power. A meta-analytical summary of smaller studies may be particularly meaningful in such cases. Smaller samples generally result in lower precision in an effect estimate, accompanied by wider confidence intervals. Because of the relevance of the assumed effect of an intervention, its size, the availability of treatment alternatives, and the frequency and severity of potential therapy-related harms, for small sample sizes it may be meaningful to accept a higher p-value than 5% (e.g. 10%) to demonstrate statistical significance, thus increasing quantitative uncertainty. Similar recommendations have been made for other problematical constellations [224]. Such an approach must, however, be specified a priori and well justified. Likewise, for small sample sizes it may be more likely that is necessary to substitute a patient-relevant outcome that occurs too rarely with surrogate endpoints. However, these surrogates must also be valid for small sample sizes [226].

In the case of extremely rare diseases or very specific disease constellations, the demand for (parallel) comparative studies may be inappropriate [760]. Nevertheless, in such cases it is also possible at least to document and assess the course of disease in such patients appropriately, including the expected course without applying the intervention to be assessed (e.g. using

historical patient data) [110]. The fact that a situation is being assessed involving an extremely rare disease or a very specific disease constellation is specified and explicitly highlighted in the report plan.

3.3 Benefit assessment of drugs

One main objective of the benefit assessment reports on drugs is to support the G-BA's decisions on directives concerning the reimbursement of drugs by the SHI. For this purpose, it is necessary to describe whether a drug's benefit has been demonstrated (or whether, when compared with a drug or non-drug alternative, a higher benefit [added benefit] has been demonstrated).

The G-BA's decisions on directives do not usually consider particular cases, but the general one. Consequently, the Institute's reports do not usually refer to decisions on particular cases.

Because of the objective of the Institute's benefit assessments, these assessments only include studies with an evidence level principally suited to demonstrate a benefit of an intervention. Thus, studies that can only generate hypotheses are generally not relevant for the benefit assessment. The question as to whether a study can demonstrate a benefit mainly depends on the certainty of results of the data analysed.

3.3.1 Relevance of the drug approval status

The commissioning of the Institute by the G-BA to assess the benefit of drugs usually takes place within the framework of the approval status of the drug to be investigated (therapeutic indication, dosage, contra-indications, concomitant treatment, etc.). For this reason, the Institute's recommendations to the G-BA, which are formulated in the conclusions of the benefit assessment report, usually refer to the use of the assessed drug within the framework of the current approval status.

It is clarified on a project-by-project basis how to deal with studies (and the evidence inferred from them) that were not conducted according to the use of a drug as outlined in the approval documents. In principle, it is conceivable that studies in which a drug was used outside the scope of the approval status described in the Summary of Product Characteristics ("off-label use"), over- or underestimated a drug's benefit and/or harm. This may lead to a misjudgement of the benefit and/or harm in patients treated within the framework of the drug's approval status. However, if it is sufficiently plausible or has even been demonstrated that the results obtained in these studies are applicable to patients treated according to the drug's approval status, these results can be considered in the benefit assessment.

Therefore, for studies excluded from the assessment only because they were off-label studies (or because it was unclear whether they fulfilled the requirements of the approval status), each case is assessed to establish to what extent the study results are applicable to patients treated according to the approval requirements.

Results from off-label studies are regarded as applicable if it is sufficiently plausible or has been demonstrated that the effect estimates for patient-relevant outcomes are not greatly affected by the relevant characteristic of the drug approval status (e.g. the pretreatment required). As a rule, the equivalence of effects should be proven with appropriate scientific studies. These studies should be targeted towards the demonstration of equivalence of the effect between the group with and without the characteristic. Results applicable to patients treated according to a drug's approval status can be considered in the conclusion of the assessment.

Results from studies are regarded as not applicable if their applicability has not been demonstrated and if plausible reasons against the transferability of results exist. As a rule, study results are regarded to be not applicable if, for example, the age range or disease severity treated lay outside the approved range or severity, if off-label combinations including other active ingredients were used, or if studies were conducted in patients with contra-indications for the intervention investigated. The results of these studies are not presented in the reports, as they cannot be considered in the assessment of the drug.

If results from off-label studies are regarded as applicable, this is specified in the report plan. As a rule the results of studies showing the following characteristics are discussed, independently of the applicability of study results to the use specified in the approval of the drug:

- They refer to patients with the disease specified in the commission.
- They refer to patients treated with the drug to be assessed.
- They are of particular relevance due to factors such as sample size, study duration, or outcomes investigated.

3.3.2 Studies on the benefit assessment of drugs

The results of the Institute's benefit assessment of drugs may have an impact on patient health care in Germany. For this reason, high standards are required regarding the certainty of results of studies included in the benefit assessment (see Section 3.1.4).

The study design has considerable influence on the certainty of results. This is because a causal association between intervention and effect cannot usually be shown with prospective or retrospective observational studies, whereas controlled intervention studies are in principle suited for this purpose [296]. This particularly applies if other factors influencing results are completely or almost completely eliminated. For this reason, an RCT represents the gold standard in the assessment of drug and non-drug interventions [538].

In the assessment of drugs, RCTs are usually possible and practically feasible. As a rule, the Institute therefore considers RCTs in the benefit assessment of drugs and only uses non-randomized intervention studies or observational studies in justified exceptional cases. A reason for exception can be the fact that other study types may also provide sufficient certainty of

results for the research question posed. For diseases that would be fatal within a short period of time without intervention, several consistent case reports, for example, may provide sufficient certainty of results that a particular intervention prevents this otherwise inevitable course [463] (dramatic effect, see also Section 3.2.2). The special obligation to justify a non-randomized design when testing drugs can also be found within the framework of drug approval legislation in the directives on the testing of medicinal products (Directive 2001/83/EC, Section 5.2.5 [436]).

In the preparation of the report plan (see also Section 2.1.1), the Institute therefore determines beforehand which study types can be regarded as feasible on the basis of the research question posed, and provide sufficient certainty of results (with high internal validity). Studies not complying with these minimum quality standards (see also Section 9.1.4) are not given primary consideration in the assessment process.

In addition to characterizing the certainty of results of the studies considered, it is necessary to describe whether – and if yes, to what extent – the study results are transferable to local settings (e.g. population, health care sector), or what local study characteristics had (or could have had) an effect on the results or their interpretation. From this perspective, studies are especially relevant in which the actual German health care setting is represented as far as possible. However, the criteria for certainty of results outlined above must not be ignored. Finally, the transferability of study results (generalizability or external validity) must be assessed in a separate process initially independent of the study design and quality.

3.3.3 Benefit assessment of drugs according to §35a SGB V

A benefit assessment of a drug according to §35a SGB V is based on a dossier of the pharmaceutical company in which the company provides the following information:

1) approved therapeutic indications
2) medical benefit
3) added medical benefit compared with an appropriate comparator therapy
4) number of patients and patient groups for whom a therapeutically relevant added benefit exists
5) cost of treatment for the SHI
6) requirements for quality-assured usage of the drug

The requirements for form and content of the dossier are outlined in dossier templates, which are a component of the G-BA's Code of Procedure [271]. In the dossier, specifying the validity of the evidence, the pharmaceutical company must describe the likelihood and the extent of added benefit of the drug to be assessed compared with an appropriate comparator therapy. The information provided must be related both to the number of patients and to the extent of added benefit. The costs for the drug to be assessed and the appropriate comparator therapy must be

declared (based on the pharmacy sales price and taking the Summary of Product Characteristics and package information leaflet into account).

The probability of the added benefit describes the certainty of conclusions on the added benefit. In the dossier, the extent of added benefit should be described according to the categories of the Regulation for Early Benefit Assessment of New Pharmaceuticals (ANV[18]) (major, considerable, minor, non-quantifiable added benefit; no added benefit proven; benefit of the drug to be assessed smaller than benefit of the appropriate comparator therapy) [106].

In the benefit assessment the validity and completeness of the information in the dossier are examined. It is also examined whether the comparator therapy selected by the pharmaceutical company can be regarded as appropriate in terms of §35a SGB V and the ANV. In addition, the Institute assesses the effects described in the documents presented, taking the certainty of results into account. In this assessment, the qualitative and quantitative certainty of results within the evidence presented, as well as the size of observed effects and their consistency, are appraised. The benefit and cost assessments are conducted on the basis of the standards of evidence-based medicine described in this methods paper and those of health economic standards, respectively. As a result of the assessment, the Institute presents its own conclusions, which may confirm or deviate from those arrived at by the pharmaceutical company (providing a justification in the event of deviation).

The operationalization for determining the extent of added benefit comprises 3 steps:

1) In the first step the probability of the existence of an effect is examined for each outcome separately (qualitative conclusion). For this purpose, the criteria for inferring conclusions on the evidence base are applied (see Section 3.1.4). Depending on the quality of the evidence, the probability is classified as a hint, an indication or proof.
2) In the second step, for those outcomes where at least a hint of the existence of an effect was determined in the first step, the extent of the effect size is determined for each outcome separately (quantitative conclusion). The following quantitative conclusions are possible: major, considerable, minor, and non-quantifiable.
3) In the third and last step, the overall conclusion on the added benefit according to the 6 specified categories is determined on the basis of all outcomes, taking into account the probability and extent at outcome level within the overall picture. These 6 categories are as follows: major, considerable, minor, and non-quantifiable added benefit; no added benefit proven; the benefit of the drug under assessment is less than the benefit of the appropriate comparator therapy.

The quality of the outcome, as well as the effect size, are essential in determining the extent at outcome level in the second step. The rationale for this operationalization is presented in the Appendix A *Rationale of the methodological approach for determining the extent of added*

[18] Arzneimittel-Nutzenbewertungsverordnung, AM-NutzenV

benefit as well as in Skipka et al. [663]. The basic approach aims to derive thresholds for confidence intervals for different effect measures depending on the effects to be achieved, which in turn depend on the quality of the outcomes and the extent categories. Depending on the quality of the outcome, the confidence interval must be completely below (in the case of relative effect sizes) or above (in the case of the standardized mean difference) a certain threshold in order to consider the extent to be minor, considerable or major.

The following 3 categories for the quality of the outcome are formed:

- all-cause mortality
- serious (or severe) symptoms (or late complications) and adverse effects, as well as health-related quality of life
- non-serious (or non-severe) symptoms (or late complications) and adverse effects

The thresholds are set separately for each category. The more serious the event, the lower the thresholds (in relation to the effect size). The higher the extent of added benefit, the higher the thresholds (in relation to the effect size).

It will not always be possible to quantify the extent at outcome level. For instance, if a statistically significant effect on a sufficiently valid surrogate is present, but no reliable estimate of this effect on a patient-relevant outcome is possible, then the (patient-relevant) effect cannot be quantified. In such and similar situations, an effect of a non-quantifiable extent is concluded, with a corresponding explanation.

On the basis of the case of a quantifiable effect, the further approach depends on the scale of the outcome. One distinguishes between the following scales:

- binary (analyses of 2x2 tables)
- time to event (survival time analyses)
- continuous or quasi-continuous, in each case with available responder analyses
- continuous or quasi-continuous, in each case with available standardized mean differences (SMDs)
- other (e.g. analyses of nominal data)

In the following text, first the approach for binary outcomes is described. The other scales are subsequently based on this approach.

A) Binary outcomes

On the basis of the effect measure “relative risk”, denominator and numerator are always chosen in such a way that the effect (if present) is realized as a value smaller than 1, i.e. the lower the value, the stronger the effect.

To determine the extent of the effect in the case of binary outcomes, the two-sided 95% confidence interval for the relative risk is used; if appropriate, this is calculated by the Institute itself. If several studies are pooled quantitatively, the meta-analytical result for the relative risk is used.

For the 3 extent categories (minor, considerable, major), the following Table 5 shows the thresholds to be undercut for each of the 3 categories of quality of the outcomes. The **upper** limit of the 95% confidence interval must be smaller than the respective threshold in order to reach the corresponding extent category.

Table 5: Thresholds for determining the extent for the relative risk

		Outcome category		
		All-cause mortality	Serious (or severe) symptoms (or late complications) and adverse effects, as well as health-related quality of life[a]	Non-serious (or non-severe) symptoms (or late complications) and adverse effects
Extent category	Major	0.85	0.75 and risk ≥ 5%[b]	Not applicable
	Considerable	0.95	0.90	0.80
	Minor	1.00	1.00	0.90

a. Precondition (as for all patient-reported outcomes): use of a validated or established instrument, as well as an appropriate response criterion.
b. Risk must be at least 5% for at least 1 of the 2 groups compared.

The relative risk can generally be calculated in 2 ways, depending on whether the risk refers to events or counter-events (e.g. survival vs. death, response vs. non-response). This is irrelevant for the statement on significance specified in Step 1 of the approach (conventional, non-shifted hypotheses), as in such a case the p-value of a single study is invariant and plays a subordinate role in meta-analysis. However, this does not apply to the distance of the confidence interval limits to the zero effect. To determine the extent of effect for each binary outcome (by means of content criteria under consideration of the type of outcome and underlying disease), it must therefore be decided what type of risk is to be assessed, that of an event or counter-event.

B) Time to event

The two-sided 95% confidence interval for the hazard ratio is required to determine the extent of the effect in the case of the outcome representing a time to event. If several studies are pooled quantitatively, the meta-analytical result for the hazard ratio is used. If the confidence interval for the hazard ratio is not available, it is approximated on the basis of the available information, if possible [707]. The same limits as for the relative risk are set for determining the extent (see Table 5).

If a hazard ratio is neither available nor calculable, or if the available hazard ratio cannot be interpreted meaningfully (e.g. due to relevant violation of the proportional hazard assumption), it should be examined whether a relative risk (referring to a meaningful time point) can be calculated. It should also be examined whether this operationalization is adequate in the case of transient outcomes for which the outcome of time to event was chosen. If appropriate, the calculation of a relative risk at a time point is also indicated here.

C) Continuous or quasi-continuous outcomes, in each case with available responder analyses

Responder analyses are used to determine the extent of added benefit in the case of continuous or quasi-continuous outcomes. For this purpose, an appropriate response criterion or cut-off value is required (see Section 9.3.3). On the basis of the responder analyses (2x2 tables) the relative risks are calculated directly from them. The extent of the effect is then determined by means of Table 5.

D) Continuous or quasi-continuous outcomes, in each case with available SMDs

In order to also assess the extent of added benefit for the effect measure SMD (Cohen's d or Hedges'g), comparable thresholds for SMDs are defined following the system of thresholds for relative risks. Orientation is provided here by the usual classification of Cohen's d into small (SMD between 0.2 and 0.5), medium (SMD between 0.5 and 0.8), and large effects (SMD 0.8) as well as the extension by Rosenthal [586], who describes the result SMD $\geq$ 1.3 as a very large effect. Furthermore, it should be kept in mind that the irrelevance threshold SMD = 0.2 has been established to ensure a relevant effect (see Section 9.3.3). Furthermore, the obvious rules of determining the extent of added benefit in the case of binary data should also apply to continuous data, namely (1) that thresholds become more stringent the greater the extent, and (2) thresholds become more stringent the less serious a symptom is (with the exception of the category "minor extent"). Based on SMD = 0.2 as the threshold for a minor added benefit for both serious and non-serious symptoms, thresholds for SMD can also be defined according to Table 6, taking into account these rules and the ranking of all thresholds according to Table 5. In contrast to the thresholds for the relative risk, it should be noted that for the SMD the 95% confidence interval must lie completely **above** the corresponding threshold and that the zero effect is not given by the number 1, but by the number 0. The **lower** limit of the 95% confidence interval must therefore be larger than the respective threshold in order to reach the corresponding extent category. It seems plausible that true small, medium and very large effects according to Cohen and Rosenthal [586] can be statistically detected by using the thresholds of Table 6 for the lower limit of the 95% confidence interval.

Table 6: Thresholds for determining the extent for the SMD

		Outcome category	
		Serious (or severe) symptoms (or late complications) and adverse effects as well as health-related quality of life[a]	Non-serious (or non-severe) symptoms (or late complications) and adverse effects
Extent category	major	0.5	Not applicable
	considerable	0.3	0.4
	minor	0.2	0.2
a. Precondition (as for all patient-reported outcomes): use of a validated or established instrument.			

E) Other outcomes

In the case of other outcomes where no responder analyses with inferable relative risks are available either, it should be examined in the individual case whether relative risks can be approximated [152] to set the corresponding thresholds for determining the extent. Otherwise the extent is to be classified as non-quantifiable.

For the third step of the operationalization of the overall conclusion on the extent of added benefit, when all outcomes are examined together, a strict formalization is not possible, as no sufficient abstraction is currently known for the value judgements to be made in this regard. In its benefit assessment the Institute will compare the conclusions on probability and on the extent of the effects and provide a justified proposal for an overall conclusion.

3.4 Non-drug therapeutic interventions

Non-drug therapeutic interventions are assessed in detail within the framework of reports (see Section 2.1.1) or rapid reports (see Section 2.1.2) or in the form of HTA reports (see Section 2.1.10). The procedure and methods of these assessments are applied according to the general principles of the methods paper. Furthermore, new examination and treatment methods that are largely based on the use of a high-risk medical device can also be evaluated within the framework of an assessment according to §137h SGB V (see Section 2.1.6). As §137h assessments are primarily based on documents submitted (and not on information retrieval conducted by the Institute itself) and have to be produced in a markedly shorter period of time, the methodological depth of the work on the assessment and the certainty of a potential conclusion on benefit or harm is as a rule lower than is the case for reports and rapid reports. In particular, §137h assessments do not distinguish between different certainties of conclusions (proof, indication, hint). However, the requirements for a benefit are the same for reports and rapid reports in comparison with assessments according to §137h SGB V and generally require the availability of RCT results on patient-relevant outcomes (see Sections 1.3.5, 3.1 and 3.2).

Even if the regulatory preconditions for the market access of drugs and non-drug therapeutic interventions differ, there is nevertheless no reason to apply a principally different standard concerning the certainty of results in the assessment of the benefits and harms of an intervention. For example, the G-BA's Code of Procedure [271] envisages, as far as possible,

the preferential consideration of RCTs, independent of the type (drug/non-drug) of the medical intervention to be assessed. The principles of evidence-based medicine and of benefit assessments are therefore also valid for specific fields of medicine, such as surgery, dentistry, psychotherapy, alternative/complementary medicine or digital health applications (e-health). For medical devices, within the framework of a conformity assessment, the RCT is not presented as the study design of choice according to the current EU Medical Device Regulation (MDR) [173], but clinical investigations must be "performed on the basis of an appropriate plan of investigation" [220], so that randomized controlled designs tend to be used more and more frequently in this area [623]. In contrast to the European conformity assessment procedure for new medical devices, the Institute's assessments always refer to examination and treatment methods, not to individual medical devices.

Compared with studies on drug interventions, studies on non-drug interventions are often associated with specific challenges and difficulties [500], but these can usually be overcome at least in part:

- Blinding of the staff performing the intervention is often impossible and blinding of patients is difficult or also impossible. However, a reduction in the informative value of a study can be mitigated by the blinded recording of outcomes or by the use of objective outcomes.
- The skills and abilities of the users of the intervention are often essential for an identifiable benefit of a non-drug intervention in a study. Both doctors and patients can be users. Ideally, adequate selection and training will help to minimize the negative impact of learning curve effects on the study results.
- Many non-drug interventions change in the course of a study. Numerous small changes (often referred to as "step-by-step innovations") are common, especially with medical devices. Changes in the intervention during the course of a study usually do not require a new study, but can be investigated in sufficient detail by using appropriate statistical methods to assess the influence of these changes on the study results.

In addition, non-drug interventions are sometimes more or less complex interventions [148]. In order to give consideration to the aspects outlined above, studies of particularly good quality are required in order to achieve sufficient certainty of results. Paradoxically, the opposite has rather been the case in the past; i.e. sound randomized studies are often lacking, particularly in the area of non-drug interventions (e.g. in surgery [500]). In order to enable any conclusions at all to be drawn on the relevance of a specific non-drug therapeutic intervention, it may therefore also be necessary to consider non-randomized studies in the assessment. Nonetheless, quality standards also apply in these studies, in particular regarding measures taken to ensure structural equality. However, such studies will usually at best be able to provide hints of a(n) (added) benefit or harm of an intervention due to their inherently lower certainty of results. The inclusion of studies with lower evidence levels is consistent with the corresponding regulation in the Chapter 2 §13 (2) of the G-BA's Code of Procedure [271]. However, the specific

obligation to provide a justification is emphasized. In this regulation it is noted: "However, in order to protect patients, recognition of a method's medical benefit on the basis of documents with lower evidence levels requires all the more justification the greater the deviation from evidence level 1 (in each case, the medical necessity of the method must also be considered). For this purpose, the method's potential benefit for patients is in particular to be weighed against the risks associated with the demonstration of effectiveness based on studies of lower informative value" [271]. This means that the non-availability of studies of the highest evidence level alone cannot generally be viewed as sufficient justification for a benefit assessment based on studies with lower evidence levels.

In the assessment of non-drug therapeutic interventions, it may also be necessary to consider the marketability or CE marking (according to the German Medical Devices Act) and the approval status of drugs (according to the German Pharmaceutical Act), insofar as the test interventions or comparator interventions comprise the use of medical devices or drugs (see Section 3.3.1). The corresponding consequences must subsequently be specified in the report plan (see Section 2.1.1).

3.5 Diagnostic tests

Diagnostic tests are characterized by the fact that their health-related benefit (or harm) is in essence only realized if the tests are followed by therapeutic or preventive procedures. The mere acquisition of diagnostic information (without medical consequences) as a rule has no benefit from the perspective of social law.

This applies in the same way both to diagnostic information referring to the current state of health and to prognostic information (or markers) referring to a future state of health. In the following text, procedures to determine diagnostic or prognostic information are therefore jointly regarded as diagnostic tests.

In general, the evaluation process for diagnostic tests can be categorized into different hierarchy phases or levels, analogously to the evaluation of drugs [1,262]. Phase 4 prospective, controlled diagnostic studies according to Köbberling et al. [1], or Level 5 studies according to Fryback and Thornbury [262] have an (ideally random) allocation of patients to a strategy with or without application of the diagnostic test to be assessed or to a group with or without disclosure of the (diagnostic) test results. These studies can be seen as corresponding to Phase 3 (drug) approval trials ("efficacy trials"). Accordingly, they are allocated to the highest evidence level (see, for example, the G-BA's Code of Procedure [271]). The US Food and Drug Administration also recommends such studies for specific indications in the approval of drugs and biological products developed in connection with diagnostic imaging techniques [718]. Examples show that they can be conducted with comparatively moderate effort [22,724].

The Institute follows this logic and primarily conducts benefit assessments of diagnostic tests on the basis of studies designed as described above that investigate patient-relevant outcomes. The main features of the assessment comply with the explanations presented in Sections 3.1 to

3.4. In this context, patient-relevant outcomes refer to the same benefit categories as in the assessment of therapeutic interventions, namely mortality, morbidity, and health-related quality of life. The impact of diagnostic tests on these outcomes can be achieved by the avoidance of high(er) risk interventions or by the (more) targeted use of interventions. If the collection of diagnostic or prognostic information itself is associated with a high(er) risk, a lower-risk diagnostic test may have patient-relevant advantages, namely, if (in the case of comparable test accuracy) the conduct of the test itself causes lower mortality and morbidity rates, or fewer restrictions in quality of life.

Conclusions on the benefit of diagnostic tests are ideally based on randomized studies, which can be conducted in various ways [68,69,244,465,486,618]. In a study with a strategy design including 2 (or more) patient groups, in each case different strategies are applied, which in each case consist of a diagnostic measure and a therapeutic consequence. A high informative value is also ascribed to randomized studies in which all patients initially undergo the conventional and the diagnostic test under investigation; subsequently, only those patients are randomized in whom the latter test produced a different result, and thereby a different therapeutic consequence, than the former test (discordance design). Studies in which the interaction between the diagnostic or prognostic information and the therapeutic benefit is investigated also have a high evidence level and should as a matter of priority be used for the benefit assessment of diagnostic tests (interaction design [618,695]). Many diagnostic or prognostic characteristics – especially genetic markers – can also be determined retrospectively in prospective comparative studies and examined with regard to a potential interaction (so-called "prospective-retrospective" design [661]). The validity of such "prospective-retrospective" designs depends especially on whether the analyses were planned prospectively (in particular also the specification of threshold values). Moreover, in all studies with an interaction design it is important that the treatments used correspond to the current standard, that the information (e.g. tissue samples) on the characteristic of interest is completely available for all study participants or at least for a sample that is clearly characterized and for which the structural equality between groups still exists, and that if several characteristics are analysed the problem of multiple testing for significance is adequately accounted for (see also Section 9.3.2) [619].

Overall, it is less decisive to what extent diagnostic or prognostic information can determine a current or future state of health, but rather that this information is of predictive relevance, namely, that it can predict the greater (or lesser) benefit of the subsequent treatment [244,662]. For this – necessarily linked – assessment of the diagnostic and therapeutic intervention it is important to note that overall, a benefit can normally only arise if both interventions fulfil their goal: If either the predictive discriminative capacity of the diagnostic intervention is insufficient or the therapeutic intervention is ineffective, a study will not be able to show a benefit of the diagnostic intervention.

Besides a strategy and interaction design, a third main form of RCTs on diagnostic questions is available with the enrichment design [487,695]. In this design, solely on the basis of the diagnostic test under investigation, only part of the patient population is randomized (and thus

included); for example, only test-positive patients, who then receive 1 of 2 treatment options. In comparison with an interaction design, such a design lacks the investigation of a potential treatment effect in the remaining patients (e.g. in the test-negative ones). Robust conclusions can thus only be drawn from such designs if, on the basis of other information, it can be excluded that an effect observed in the randomized patient group could also have existed in the non-randomized group.

In specific cases an interaction between the diagnostic or prognostic marker and the treatment effect can be inferred with sufficient certainty, even if the treatment effect is only known for the whole group (i.e. test-positive and test-negative persons together). In the (theoretically) extreme case, a test result allows certain exclusion of the disease, so that the treatment of a disease is useless and at most produces side effects. However, statistically it cannot be demonstrated with absolute certainty that a certain test result indicates or excludes a certain health state. But if it can be shown for a test in this situation that test-negative persons have a sufficiently low (or test-positive persons a sufficiently high) risk of reaching key outcomes, then, under consideration of a treatment's benefit and harm, the test can allow a sufficiently certain decision against (or for) a treatment [552]. For example, a treatment that has a positive benefit-harm ratio in the overall group of patients might not be meaningful in a subgroup of test-negative patients, because the (absolute) treatment effect in this low-risk group can at most be negligibly small. For such a linked observation of the treatment effect in the overall group and the outcome risk in a subgroup to be sustainable, it must be excluded with sufficient certainty that the (relative) treatment effect in the subgroup differs markedly from that in the overall group. Furthermore, data on patient preferences can be considered in order to specify appropriate thresholds for the assessment of the benefit-harm ratio. In addition, it can be meaningful to specify a topic-specific minimum size (expressed as a percentage) of the subgroup of test-negative or test-positive persons.

The comments above primarily refer to diagnostic tests that direct more patients towards a certain therapeutic consequence by increasing the test accuracy (i.e. sensitivity, specificity or both). In these cases, as a rule it is necessary to examine the impact of the diagnostic test on patient-relevant outcomes by covering the whole diagnostic and therapeutic chain. However, it is possible that the diagnostic test under investigation is only to replace a different and already established diagnostic test, without identifying or excluding additional patients. If the new test shows direct patient-relevant advantages, for example, is less invasive or requires no radiation, it will not always be necessary to re-examine the whole diagnostic-therapeutic chain, as the therapeutic consequences arising from the new test do not differ from those of the existing test [58,69,505]. To demonstrate benefit, in these cases test accuracy studies could be sufficient in which it is shown that the test result of the test under investigation (= index test) agrees with that of the existing test (= reference test) in a sufficiently high proportion of patients (one-sided question of equivalence). This question on the (non-)agreement of test results in individual patients is also known as the concordance question.

For a comparison of 2 or more diagnostic tests with regard to certain test accuracy characteristics the highest certainty of results arises from cohort or cross-sectional studies in which the diagnostic tests are conducted independently of one another in the same patients and the test results are assessed under mutual blinding [466,751]. Additionally, in patients with rapidly progressing diseases, a random sequence of the conduct of the tests can be important. Besides studies that allow an intra-individual comparison of test results, RCTs are also conceivable where in each case one part of the patient population is only examined with the one or the other index test before preferably all results are verified by means of a uniform reference test. Similar to other study designs, this study design allows the determination of test accuracy characteristics with the highest certainty of results.

If a study is to provide informative data on the benefit, diagnostic quality or prognostic value of a diagnostic test, it is essential to compare it with the previous diagnostic approach [697]. Only in this way can the added value of the diagnostic or prognostic information be reliably determined. For studies on test accuracy this means that, besides sensitivity and specificity of the new and previous method, it is of particular interest to what extent the diagnostic measures produce different results per patient (see concordance question above).

In contrast, in studies on prognostic markers multifactorial regression models often play a key role, so that Section 9.3.6 should be taken into account. When selecting non-randomized designs for diagnostic methods, the ranking of different study designs presented in Section 9.1.3 should as a rule be used.

In the assessment of the certainty of results of diagnostic accuracy studies, the Institute primarily follows the QUADAS-2[19] criteria [750,751], which, however, may be adapted for the specific project. The STARD[20] criteria [71,72] are applied in order to decide on the inclusion or exclusion of studies not published in full text on a case-by-case basis. The PROBAST[21] instrument [762] is primarily used for the methodological assessment of prognosis studies. The criteria of the TRIPOD[22] statement [140] are used to decide whether to include or exclude studies not published in full text [16,20,337,338,504,660,737].

Level 3 and 4 studies according to Fryback and Thornbury [262] are to investigate the effect of the (diagnostic) test to be assessed on considerations regarding (differential) diagnosis and/or subsequent therapeutic (or other management) decisions, i.e. it is investigated whether the result of a diagnostic test actually leads to any changes in decisions. However, such studies or study concepts have the major disadvantage that they are not sharply defined, and are therefore of rather theoretical nature. A principal (quality) characteristic of these studies is that it was clearly planned to question the physicians involved regarding the probability of the existence of the

[19] Quality Assessment of Diagnostic Accuracy Studies

[20] Standards for Reporting of Diagnostic Accuracy

[21] Prediction Model Risk Of Bias Assessment Tool

[22] Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

disease (and their further diagnostic and/or therapeutic approach) *before* the conduct of the diagnostic test to be assessed or the disclosure of results. This is done in order to determine the change in attitude caused by the test result. In contrast, retrospective appraisals and theoretical estimates are susceptible to bias [262,311]. The relevance of such ultimately uncontrolled studies within the framework of the benefit assessment of diagnostic (or prognostic) tests must be regarded as largely unclear. Information on management changes alone cannot therefore be drawn upon to provide evidence of a benefit, as long as no information on the patient-relevant consequences of such changes is available.

It is also conceivable that a new diagnostic test is incorporated in an already existing diagnostic strategy; for example, if a new test precedes (triage test) or follows (add-on test) an established test in order to reduce the frequency of application of the established test or new test, respectively [68]. However, against the background of the subsequent therapeutic (or other types of) consequences, it should be considered that through such a combination of tests, the patient populations ensuing from the respective combined test results differ from those ensuing from the individual test results. This difference could in turn influence subsequent therapeutic (or other types of) consequences and their effectiveness. If such an influence cannot be excluded with sufficient certainty – as already described above – comparative studies on diagnostic strategies including and excluding the new test may be required [472,718].

Several individual diagnostic tests or pieces of information are in part summarized into an overall test via algorithms, scores, or similar approaches. In the assessment of such combined tests the same principles should be applied as those applied for individual tests. In particular, the validation and clinical evaluation of each new test must be performed independently of the test development (e.g. specification of a threshold, weighting of scores, or algorithm of the analysis) [681].

Biomarkers used within the framework of personalized or better stratified medicine should also be evaluated with the methods described here [353,695]. This applies both to biomarkers determined before the decision on the start of a treatment (or of a treatment alternative) and to those determined during treatment in order to decide on the continuation, discontinuation, switching, or adaptation of treatment [666,723]. Here too, it is essential to distinguish between the prognostic and predictive value of a characteristic. Prognostic markers provide information on the future state of health and normally refer to the course of disease under treatment and not to the natural course of disease without treatment. The fact that a biomarker has prognostic relevance does not mean that it also has predictive relevance (and vice versa).

Finally, in the assessment of diagnostic tests, it may also be necessary to consider the result of the conformity assessment procedure for CE marking and the approval status of drugs used in diagnostics (see Section 3.3.1). The corresponding consequences must subsequently be specified in the report plan (see Section 2.1.1).

3.6 Early diagnosis and screening

Screening programmes are composed of different modules, which can be examined either in part or as a whole [157,657]. The assessment of a screening test generally follows internationally accepted standards and criteria, for example, those of the UK National Screening Committee (UK NSC [568])), the US Preventive Services Task Force (US PSTF [323,558,624]), or the New Zealand National Health Committee (NHC) [520].

According to the criteria outlined above, the Institute primarily assesses the benefit of screening tests by means of prospective comparative intervention studies on the whole screening chain, which include the (ideally random) allocation of participants to a strategy with or without application of the screening test (or to different screening strategies) and which investigate patient-relevant outcomes. In this context, the main features of the assessment comply with the explanations outlined in 3.1 to 3.1.4.

If such studies are not available or are of insufficient quantity or quality, an assessment of the single components of the screening chain can be performed. In this context, the accuracy of the diagnostic test is assessed by means of generally applied test accuracy criteria, determined in studies showing sufficient certainty of results (usually Phase 3 according to Köbberling et al. [1]) (see Section 3.5), and it is reviewed to what extent it is proven that the consequences resulting from the test outcomes are associated with a benefit. In the case of therapeutic consequences (which are mostly assumed), proof can be inferred from randomized intervention studies in which an early (earlier) intervention was compared with a late(r) one. The benefit of an early (earlier) vs. a late(r) intervention may also be assessed by means of intervention studies in which the interaction between the earliness of the start of the intervention and the intervention's effect can be investigated. This can be performed either directly within a study or indirectly by comparing studies with different starting points for the intervention, but with otherwise comparable study designs. Here too, the main features of the assessment comply with the explanations outlined in Sections 3.1 to 3.1.4.

A particular aspect of harm from screening is the fact that screening produces overdiagnoses. An overdiagnosis is defined as an actually true-positive diagnosis which, however, without screening would not have caused symptoms during a person's life [126]. For instance, overdiagnoses occur in screening for slowly progressing diseases, because in these cases, there is a high probability that a person will die of a different cause before developing symptoms. Since overdiagnoses are inevitable as a harmful effect of any screening, but can only be recorded indirectly, specific methods for recording this outcome are required [125,218].

3.7 Prevention

Prevention is directed at avoiding, reducing the probability of, or delaying health impairment [741]. Whereas primary prevention comprises all measures employed before the occurrence of detectable biological impairment in order to avoid the triggering of contributory causes, secondary prevention comprises measures to detect clinically asymptomatic early stages of

diseases, as well as their successful early therapy (see also Section 3.6). Primary and secondary prevention measures are characterized by the fact that, in contrast to curative measures, whole population groups are often the focus of the intervention. Tertiary prevention in the narrowest sense describes specific interventions to avoid permanent (especially social) functional deficits occurring after the onset of disease [341]. This is not the focus of this section, but is addressed in the sections on the benefit assessment of drug and non-drug interventions (see Sections 3.3 and 3.4).

The Institute also primarily performs benefit assessments of prevention programmes (other than screening programmes) by means of prospective, comparative intervention studies that have an (ideally random) allocation of participants to a strategy with or without application of the prevention measure, and that investigate patient-relevant outcomes. Alternatively, due to potential contamination between the intervention and control group, studies in which clusters were allocated to the study arms may also be eligible [708].

In individual cases, it needs to be assessed to what extent the consideration of other study designs is meaningful [396]. For example, mass-media campaigns are often evaluated within the framework of interrupted time-series analyses (e.g. Vidanapathirana et al. [731]), and the use of this study design is also advocated for community intervention research [59]. In the quality assessment of these studies, the Institute uses for orientation the criteria developed by the Cochrane Effective Practice and Organisation of Care Review Group [139].

For the benefit on the population level, not only the effectiveness of the programme is decisive, but also the participation rate. In addition, the question is relevant as to which persons are reached by prevention programmes; research indicates that population groups with an increased risk of disease participate less often in such programmes [447]. Special focus is therefore placed on both of these aspects in the Institute's assessments.

3.8 Assessments of potential and §137h assessments

The following text first addresses assessments of potential according to §137e SGB V, before assessments according to §137h SGB V are explained. The common feature of both assessment procedures is that certain non-drug examination or treatment methods are assessed on the basis of documents submitted to the Institute by external third parties. Another common feature of both assessment procedures is that they can lead to the conduct of a testing study. The study's key points must therefore be reviewed or developed by the Institute itself.

3.8.1 Assessments of potential

In contrast to benefit assessments, assessments of potential according to §137e SGB V aim to investigate whether new examination or treatment methods potentially show a benefit. In this context, "potential" means that firstly, the evidence available so far indicates that a potential benefit may exist, and secondly, that on the basis of this evidence a study can be planned that

allows an assessment of the benefit of the method on a sufficiently reliable evidence level; see Chapter 2 §14 (3, 4) of the G-BA's Code of Procedure [271].

An assessment of potential according to §137e (7) SGB V is based on an application for which the G-BA has defined the form and required content. Those entitled to apply are manufacturers of a medical device on which the technical application of a new examination or treatment method is largely based, as well as companies that in another way as a provider of a new method have an economic interest in providing their service at the expense of the health insurance funds. The application must contain informative documents especially referring to the current evidence on and the expected benefit of the new examination and treatment method (see §20 (2) No. 5 of the G-BA's Code of Procedure [271]). Optionally a proposal can be submitted on the key points of a testing study. An application for a method can refer to one or several therapeutic indications.

Within the framework of the assessment of potential the Institute evaluates the plausibility of the information provided by the applicant. This evaluation especially refers to the meaningfulness of the medical question(s) presented in the application, the quality of the information retrieval conducted by the applicant (see Section 8.5), the assessment of the certainty of results of the relevant studies, and the correctness of the results presented in the application. The Institute can conduct its own literature searches to support the assessment; however, it is not the Institute's responsibility or goal to complete the documents presented. The assessment leads to a conclusion on the potential of the examination or treatment method applied for. If a potential is determined from the Institute's point of view, the testing study proposed by the applicant is evaluated; if the application does not contain such a proposal or an unsuitable one, the Institute specifies the key points of a possible testing study. If the existing (or soon to be expected) evidence indicates that a benefit assessment is already meaningfully possible even without a testing study, the report refers to this and does not describe a testing study.

Due to the particular aim, considerably lower requirements for the evidence are imposed in assessments of potential compared with benefit assessments. Ultimately, the aim of testing is first to generate an adequate data basis for a future benefit assessment. Accordingly, a potential can be justified, in particular also on the basis of non-randomized studies. Moreover, further methodological principles of benefit assessments are not used or only used to a limited extent in assessments of potential, as described in the following text.

In contrast to benefit assessments, due to lower requirements for the evidence, in assessments of potential an extended assessment of the qualitative certainty of results of non-randomized studies is performed. In this context, besides the categories mentioned in Section 3.1.4 for randomized studies (high or moderate certainty of results) the following categories are used:

- **low qualitative certainty of results:** result of a higher quality non-randomized comparative study with adequate control for confounders (e.g. quasi-randomized

controlled studies, non-randomized controlled studies with active allocation of the intervention following a preplanned rule, prospective comparative cohort studies with passive allocation of the intervention),

- **very low qualitative certainty of results:** result of a higher quality non-randomized comparative study (see point above), but without adequate control for confounders or result of another non-randomized comparative study (e.g. retrospective comparative cohort studies, historically controlled studies, case-control studies),
- **minimum qualitative certainty of results:** result of a non-comparative study (e.g. one-arm cohort studies, observational studies or case series, cross-sectional studies or other non-comparative studies), which allows an indirect comparison with the results of other studies (literature controls).

An important aspect of the certainty of results is the control for confounders, which can in particular be achieved through the use of multifactorial statistical methods – as described in Section 9.3.6. Further factors are also taken into account in the assessment of the certainty of results (see Section 9.1.4).

Deviating from the procedure aimed at inferring conclusions on benefit in terms of proof, indications or hints (see Section 3.1.2), in assessments of potential, surrogate endpoints are also considered for which no sufficient validity has yet been shown. However, surrogate endpoints should be established and plausible so as to be able to justify a potential.

If the potential of diagnostic methods is to be evaluated, data on test accuracy are also considered. In this context, the certainty of results of the underlying studies must be examined (see Sections 3.5 and 9.3.13). In a second step, an evaluation of the plausibility of the diagnostic method is performed with regard to the effects postulated by the applicant in respect of patient-relevant outcomes, that is, possible direct effects of the method, as well as therapeutic consequences via which the diagnostic method could influence patient-relevant outcomes.

3.8.2 §137h assessments

In §137h assessments, the basis of the assessment is not an application by a medical device manufacturer or another company, which is the case for the procedure following §137e SGB V; assessments according to §137h SGB V are based on documents compiled by a hospital. The assessment refers to a new examination or treatment method whose technical application is largely based on the use of a high-risk medical device. The hospital must reach an agreement with the medical device manufacturer before submitting the information on the benefit of the method to the G-BA. This information can then be supplemented at the G-BA by further hospitals and medical device manufacturers before being forwarded to IQWiG for assessment.

A §137h assessment can lead to 3 possible outcomes according to §137h (1) Sentence 4 SGB V:

- The method to be assessed shows a benefit in terms of §137h (1) Sentence 4 SGB V. In this case, there is no need to deal with a possible testing study.
- The harmfulness or ineffectiveness of the method to be assessed can be identified in terms of §137h (1) Sentence 4 SGB V. In this case, too, there is no need to deal with a possible testing study.
- Neither the benefit nor the harmfulness nor the ineffectiveness of the method can be identified. In this case, the key points of a possible testing study must be examined or newly developed.

The assessment of the first 2 items (identifiable benefit, harmfulness) follows the principles described in Section 3.1. Harmfulness corresponds to greater harm from the new method compared with no treatment. Ineffectiveness consists of the new method recognizably showing only effects comparable to those of no treatment. For this purpose, in addition to results on patient-relevant outcomes, results on surrogate outcomes may be sufficient.

4 Health economic evaluation of medical interventions

4.1 Introduction

According to SGB V, in relation to the specific commission the Institute determines the methods and criteria for the preparation of HEEs on the basis of the international standards of evidence-based medicine and health economics recognized by the respective experts in these fields. For each HEE, decisions must be made, among other things, on the perspective, the time horizon, the choice of comparators, the underlying care pathway, the model, the data basis, and the presentation of uncertainty. These basic criteria for an HEE are briefly explained against the background of commissioning by the G-BA. All deviations from the methods presented here must be justified in the individual case.

4.1.1 Legal basis for a health economic evaluation according to SGB V

In the following cases, the Institute can be commissioned with health economic research questions:

- According to §139a (3) No. 2 SGB V, the Institute can be commissioned with regard to questions concerning the quality and efficiency of services provided within the framework of statutory health insurance (SHI).
- HEEs of drugs can also be commissioned by the G-BA according to §35b SGB V.
- Furthermore, an HEE can be commissioned by the Federal Ministry of Health according to §139b (2) SGB V.

In the following text, at first methodological aspects generally applying to HEEs are addressed. In Section 4.9 the deviations are explained that arise from HEEs of drugs performed according to §35b SGB V.

4.1.2 Perspective

Depending on the commission, the following perspectives can be considered: the (pure) perspective of SHI, the perspective of the community of SHI insurants (short: “SHI insurant perspective”), the social insurance perspective or the perspective of individual social insurance branches, as well as the societal perspective. In contrast to the pure SHI perspective, in the SHI insurant perspective the costs borne by the insurants (e.g. from co-payments) are also considered (see Section 4.4.1). Depending on the commission, it can be required for an HEE to consider the perspective of individual social insurance branches in addition to the SHI insurant perspective. The decision on whether further perspectives are included in an HEE depends solely on the question as to whether this is relevant for the decision maker. The results of the assessment from an extended perspective are presented separately to the decision maker.

4.1.3 Time horizon

The time horizon must at least represent the average study duration and thus consider the differences in costs and benefits between the interventions of an HEE that are relevant for the decision. A longer time horizon should preferably be chosen in particular for chronic diseases [89,200,485,709]. Decision-analytic models are often applied for health economic evaluations over longer time horizons [653]. Costs and benefits should always be modelled over the same time horizon.

The appropriate time horizon is often longer than the period covered by the available primary data from prospective studies. In these cases, under consideration of the duration of the studies, a time horizon appropriate for the disease should be chosen [345,709].

4.1.4 Choice of comparators

For the derivation of an efficiency frontier, the presentation form chosen by the Institute for results of an HEE (see Section 4.6), all healthcare-relevant interventions in a therapeutic area should be considered in an HEE. Active ingredients can, for example, be pooled into drug classes, if this seems meaningful from a medical point of view and if homogeneity is sufficient (see Section 9.3.7).

4.1.5 Care pathway

For each HEE, at first one or more care pathways should be developed for the therapeutic area. A care pathway describes treatment processes for patients with one or more specific therapeutic indications in a chronological sequence and structures them according to sectors, professions involved, stages, and, if applicable, further aspects. This care pathway serves as a basis for developing the decision-analytic model (see Sections 4.1.6 and 4.2). Furthermore, the literature searches for data on costs and further data required for the model are also based on the care pathway.

At first, for each specific commission the course of disease and the provision of health care in Germany should be briefly described for the relevant therapeutic indication, together with the sources used. The relevant interventions and treatment steps in the different areas of service, including the service providers, must be rendered within the limits of the approval status and the efficiency principle. Moreover, their application must be evaluated within the specifications of the directives and treatment advice that apply in the SHI system. Furthermore, the current treatment recommendations for Germany should be presented, using valid (clinical practice) guidelines. The relevant components for the HEE should be distinguished from the health care context described, so that a care pathway relevant to the model can be described. If individual components are specifically not included in the care pathway, this decision should be justified.

A piggy-back study is a clinical study in which, in addition to the determination of the benefits and harms of a health technology, the costs are also simultaneously determined. Even if such a study is available, concomitantly a care pathway should also be depicted, so that the costs and

further data collected in the piggy-back study can be comprehended by means of the attached care pathway.

4.1.6 Model

Piggy-back studies are very rarely available. Moreover, economic data are mostly not collected in clinical studies. The data are often insufficient to comprehensively analyse the costs of an intervention. This is because on the one hand, clinical studies rarely provide information on the long-term economic consequences accompanying the introduction of a new intervention. On the other, they do not always adequately and completely address the health care aspects relevant for the cost side in Germany. Moreover, a protocol-induced use of resources within the context of clinical studies can also induce misjudgements on the cost side. For these reasons, the modelling of the costs of an intervention is an important component of an HEE (see Section 4.4). Likewise, in an HEE the benefit can be modelled if a longer time horizon than the one used in the underlying studies is supposed to be used in the HEE (see Section 4.3).

4.1.7 Specific data sources of health economics

Data considered in the HEE to illustrate the provision of health care, epidemiology, and costs, can be collected in various ways and originate from various sources (see also Sections 4.4.4 and 4.5.2).

Analyses of secondary data should follow guidelines and recommendations on the good practice of secondary data analysis [25]. In particular, the choice of data basis, the size and relevant characteristics of the sample and the study population (incl. inclusion and exclusion criteria), the statistical methods, and the control of confounding factors, should be described transparently and justified. The generalizability and representativeness of results should be explained. The individual analysis steps must be comprehensible; plausibility checks should be ensured.

If guidelines are used, they should be evidence-based and originate from the German health care system or from an Organization for Economic Co-operation and Development (OECD) country with health care structures comparable to Germany (see Sections 5.2.2 and 5.2.3). If no evidence-based guidelines are available in the therapeutic area to be assessed, it is to be considered and presented transparently whether other German guidelines can be used or whether expert surveys should be drawn upon.

Expert surveys follow the generally recognized methods and procedures of quantitative social research. This means that in expert surveys, explicit information should be provided on the recruitment, number and expertise of experts, the research question, individual answers (not only mean values), the manner of achieving a consensus, as well as on the presentation and handling of results. Price catalogues or lists must be current and represent the prices relevant for the SHI.

4.1.8 Uncertainty

Following common international practice, one distinguishes between the following types of uncertainty in health economic decision analysis [82]:

Table 7: Concepts of uncertainty in health economic decision analysis[a]

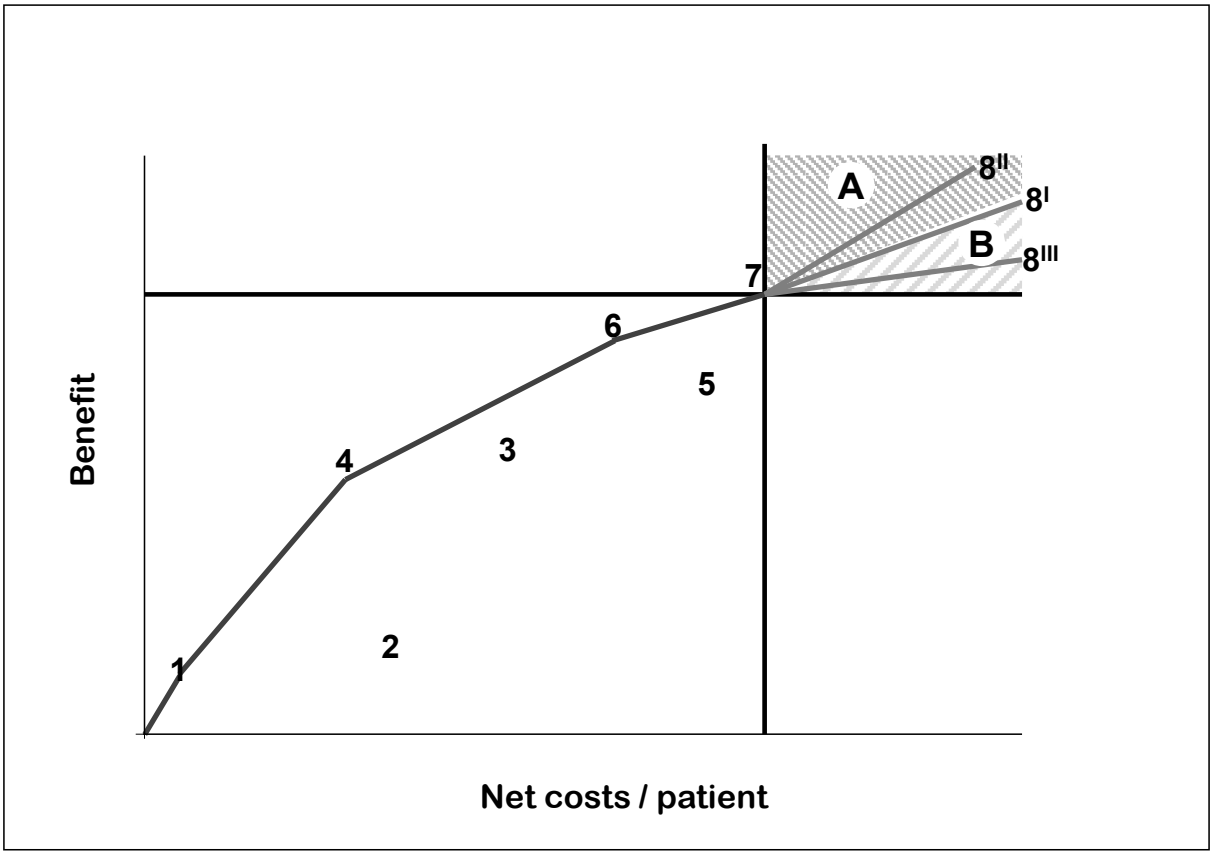
Term	Concept	Other terms sometimes employed	Analogous concept in regression
Stochastic uncertainty	Random variability in outcomes between identical patients	Variability, first-order uncertainty	Error term
Parameter uncertainty	The uncertainty in estimation of the parameter of interest	Second-order uncertainty	Standard error of the estimate
Structural uncertainty	The assumptions inherent in the decision model	Model uncertainty	The form of the regression model (e.g., linear, log-linear)
a. Table content = extract from Briggs et al. [82].			

Due to the complexity of an HEE, the investigation of uncertainty must be considered in all areas. For this purpose, the Institute follows the classification of uncertainty (see Table 7).

To this end, at first basic comments on uncertainty and the distribution assumptions are made in Sections 4.2 to 4.5. The conduct and presentation of the investigation of uncertainty are then presented in Section 4.7.

4.1.9 Interpretation of results

The results are presented in tables and graphs in the form of an efficiency frontier (see Figure 11). Interventions 1 to 7 are plotted as comparators with their cost-effectiveness ratios. Interventions 1, 4, 6, and 7 form an efficiency frontier. The last segment of the efficiency frontier can be linearly extrapolated on the assumption that it represents the reciprocal of the current willingness-to-pay. Then the following applies: Interventions that, related to an outcome, lie on Area A (see Intervention 8^{II}) have, according to their cost-effectiveness ratio, a better cost-effectiveness ratio versus the extrapolated last segment of the efficiency frontier and can thus be reimbursed at the price specified. Interventions on Area B (see Intervention 8^{III}) have, according to their cost-effectiveness ratio, a less favourable cost-effectiveness ratio versus the extrapolated last segment of the efficiency frontier, so that their price based on the efficiency frontier can be regarded as inappropriate, since the existing efficiency would deteriorate. Under consideration of the criterion of the appropriateness of the costs of interventions on Area B, the decision maker can negotiate a reimbursement price. Interventions with a constant cost-benefit relation (see Intervention 8^{I}) also fulfil the criterion that their price would be appropriate in comparison with the extrapolated last segment of the efficiency frontier.



Net costs = costs arising from health care, adjusted by cost savings, so-called cost offsets.

Figure 11: Presentation of the areas relevant to decisions

The efficiency frontier illustrates which interventions show the comparatively greatest benefit in relation to the costs incurred. Inefficient interventions are, for example, both more expensive and in relation to an outcome of lesser benefit than other interventions. If both costs and the benefit generated by the new intervention are higher than those already depicted in the efficiency frontier, the costs appropriate for this intervention are not directly inferable from the efficiency frontier itself. Further criteria must thus be drawn upon to assess whether the use of a new treatment that produces an added benefit, but is also more cost-intensive, is appropriate. The Institute assumes that the deterioration of efficiency in a therapeutic indication through inclusion of new interventions is inappropriate. This efficiency is implemented through the linear extrapolation of the gradient of the last segment of the efficiency frontier. Hence, in the event of a given benefit of an intervention under assessment, those cost-effectiveness ratios are regarded to be appropriate that, as measured by the efficiency frontier, do not lead to a deterioration of efficiency in a given therapeutic area (see Figure 11).

If a measure of the overall benefit is specified (see Section 4.3.3), this is to be regarded as the primary result. If the determination of several efficiency frontiers is required for the assessment of an intervention, the decision maker is entitled to conduct a weighting of results, under observation of the relevance of patient-relevant outcomes. A similar approach can also be considered for the approval of an intervention in several therapeutic areas.

The reasonableness of cost coverage by the community of SHI insurants depends on the one hand on the appropriateness of an intervention's price, but on the other, also on the associated future overall costs depending on the financial capacity and willingness-to-pay of the community of SHI insurants. As neither the financial capacity nor the willingness-to-pay of the community of SHI insurants is assessed, no specific recommendation is issued on the reasonableness of cost coverage. To depict the future financial impact of a cost coverage, a budget impact analysis should be conducted that can serve as an information basis for the decision maker concerning the decision on reasonableness.

4.2 Modelling

4.2.1 Basic principles

In a health economic decision model as the key component of an HEE, data on benefits and costs are merged from different sources in order to calculate the cost-effectiveness ratios of interventions during the course of the disease. Merging of data from different sources by means of a model is often required for numerous reasons. In most cases not all variables relevant for the decision are recorded in a study. A health economic model is also explicitly used to extrapolate benefits and costs beyond the period covered by a study.

Health economic models, like mathematically-formalized models, are thus a simplified depiction of reality. Moreover, analytic clarity is achieved by intentionally reducing complexity to the decision factors and variables relevant for the decision problem.

Thorough documentation is of key importance for health economic models. This documentation should generally consist of 2 parts: on the one hand, a general descriptive documentation of the approach, in which the decisions made and the data (sources) chosen are presented and justified, and on the other, a technical documentation in which the functional/mathematical relations of the model components are presented, so that an expert third party can replicate the results of the model independently of a specific software.

The degree of complexity or the degree of the reduction of a model always depends on the research question posed and cannot be specified a priori. For this reason, besides the internal validity of a model, the applicability should be described and proven. The model structure (e.g. health states), which must be covered by the approval status of the intervention and the framework of the provision of services according to SGB V, is as a rule developed in agreement with external clinical experts to ensure external validity.

4.2.2 Basic aspects of model development

The results of the models must provide a detailed depiction of the benefits and costs incurred in Germany for the intervention under assessment. For this purpose, the following information must be included in the model:

- results on effects (benefits and harms) of the interventions

- complete recording of disease costs and
- all aspects of the disease and treatment that may have a relevant impact on the benefit or cost components of the model, e.g. in the areas of demographics, epidemiology, and care pathway(s)

As data on individual aspects are often lacking, it is particularly important to explore the impact of assumptions and of the model input on the results by means of sensitivity analyses.

The following conditions must be fulfilled to ensure the validity and formal/content-related comprehensibility of a model:

- complete transparency with clearly described and justified model input and assumptions
- sufficient depth to adequately depict the disease modelled as well as the associated costs and the respective care pathways
- sufficient flexibility to calculate multiple scenarios for varying assumptions and settings
- option of determining uncertainty in the predicted cost and benefit components

4.2.3 Influence diagram and model concept

On the basis of deliberations and information leading to the creation of the care pathway, the basic principles of the model are presented in an influence diagram and a model concept.

An influence diagram graphically depicts the essential relationships of the model between the course of the disease, the patient characteristics, the pathophysiological processes, and the treatment. It displays the factors that have or might have an influence on the research question(s) to be modelled. Despite its name, the influence diagram does not per se show causal associations.

The model concept is based on the influence diagram and presents the intended design in much greater depth. As even the most sophisticated models are simplifications of reality, with required assumptions and limitations referring to the content included [7,200], the model can only be properly understood if the model concept is specified and documented in a comprehensible manner.

4.2.4 Data basis

Published models can be used as a basis for a model concept. These are identified within the framework of a focused information retrieval on health economic evaluations. For the creation of the impact diagram an exploratory search is conducted, among other things, for German guidelines in the therapeutic area investigated (see Section 4.1.7). Results of expert surveys or an analysis of SHI routine data can be considered as supplementary information.

4.2.5 Choice of modelling technique

The choice of the appropriate modelling technique depends on the research question posed, the characteristics of the intervention under assessment, the respective disease, and the general framework. When choosing the modelling technique the guiding principle for the Institute is that the economic model should be as sophisticated and complex as required to adequately answer the research question(s) posed. The evidence base itself should not determine the choice of modelling technique. If the choice of a modelling technique requires a modification of the model concept, this choice should be re-evaluated [114].

The modelling technique chosen must also be compared with those techniques already conducted/published for the same or closely related decision problems. If the model applied deviates from the models already existing, this should be discussed and justified. However, as the appropriate modelling technique always depends on the underlying research question, fixed requirements specified a priori are not meaningful, the more so as the international standard of health economics is being continuously further developed [386]. As a matter of principle, the following key problem areas should be considered:

- Temporal dimension: For which time horizon are conclusions drawn and extrapolations performed, and how is time structured within the model (e.g. continuously/discretely, length of cycle)?
- Analysis unit: Which analysis or experimental unit is depicted (e.g. individuals, cohorts) and which characteristics are considered (age, sex, etc.)?
- Interactions: Which interaction is depicted between the analysis units themselves (i.e. patients) or other elements of the model?

As data from different sources are often merged for modelling, it might be necessary to transform these data into the same format, e.g. relating to the same period of time.

4.2.6 Model documentation and model validation

A) Model validation and structural uncertainty

A simulation model that is valid for one research question might not be valid for another [453]. The external validation process must therefore cover each intended use of the model and, if used for other research questions, the model must be validated again. There is disagreement on the appropriate approach for model validation; however, there are some basic steps that must be followed [620].

A key element of validation addresses the question as to whether the model adequately depicts the reality of the course of the disease and of treatment. The plausibility check (face validity) refers to the influence diagram, the model concept, data acquisition, the processing of functional relationships, and the choice of modelling technique.

A further key element of validation is the correct technical implementation of the model (internal or technical validation). This aspect refers to the question as to whether the technical implementation actually implements the model concept correctly, for example, whether the results are numerically correct and robust.

A third element of validation is the predictive validity: To what extent does the model predict the future, that is, are the predicted results reflected in the "real world"? This is certainly the most desirable form of validity, but the most difficult to prove, if at all possible [727]. However, a comparison of the model's results with previous, comparable studies is meaningful and differences should be explicable. This also applies to comparisons with other health economic models (cross validity).

A specific form of uncertainty in model development or validation is the so-called structural uncertainty, with regard to which it is scrutinized to what extent the functional relationships underlying the model are actually valid and whether other functional forms would not be more appropriate. If it becomes obvious in the planning and development of a model that the structural uncertainty is relevant for the underlying research question, it may be necessary to develop several (alternative) models in order to quantify the consequences of this form of uncertainty on the result [694].

B) General documentation

A detailed technical report must be prepared describing all the modelling steps from the development of the influence diagram to the final validation. In addition, a fully executable version of the model must be made available, along with a user manual. In line with recommendations from guidelines [336,523,742], the documentation of the model should include the following:

- The influence diagram used to guide model development.
- Details of the model concept:
  - description of the target population(s) considered in the evaluation, including subgroups
  - description of the interventions evaluated
  - choice of the model settings (simulation size, time horizon, discounting rates, etc.) and justification
  - overview of current health economic evaluations in the therapeutic area investigated.
- Description of all data sources. Justification for choice of data sources must be provided.
- Details of all functional relationships used in the model. If they were custom-developed for the model, detailed information on the methods used must be provided.

- Listing of all assumptions with regard to data sources and model structure. Especially important is a detailed account of any assumption and technique used to project beyond the period to which the data apply.
- Rationale for the modelling technique adopted
  - description of how the technique conforms to the required features.
- Overview of the validation techniques used and their results.
- Detailed presentation of results, including an assessment of the impact of the
  - use of the intervention in relevant subgroups
  - uncertainty in input data (see Section 4.7 on sensitivity analyses).
- Interpretation of the results, including a description of the limitations of the approach used.

C) Technical documentation and electronic version of the model

The technical documentation is crucial for the understanding and the assessment of the underlying health economic model. All variables used should be named and defined. The functional/mathematical relationships of the model components should be presented and, if applicable, justified. The formal-mathematical relationships should connect all input variables considered in the model (e.g. health states) with the respective operators (e.g. age-specific transition probabilities). In addition, the derivation of interim and final values must still be presented.

All calculation steps within the software should be documented in a comprehensible manner. This is generally performed by documentation of the program code with which the electronic version of the model is implemented. In table calculation programs (e.g. Excel), the sequence of the calculation steps cannot be directly obtained from the electronic version. If applicable, these steps must then be documented in writing in a way that the sequence of the calculation steps is evident.

An electronic version of the model must be made available under the precondition that the model will be made publicly available and, if required, can be adapted for future evaluations. The electronic version of the model must be fully accessible and enable the reviewers, as well as the public, to view all formulae and relationships used in the model and to execute the model with different input data. To facilitate the review of the model, the electronic version should include a user manual describing which software and hardware is required, how the inputs into the model can be changed, how these inputs can be found in the model, how the model can be executed, and how results can be extracted.

4.3 Benefit

The methods used to determine the benefit of interventions within the framework of benefit assessments are described in Chapter 3. If the time horizon of the HEE is longer than the one

used in the studies that are included in the benefit assessment, the benefit proven by studies is to be distinguished from the modelled benefit.

4.3.1 Transfer and presentation of the benefit

For the integration of the benefit into the HEE by means of the efficiency frontier, the benefit needs to be approximately cardinally scaled. In the HEE the approximately cardinally scaled benefit (derived directly from study results when applicable) or a transformed approximately cardinally scaled benefit can be plotted on the vertical axis. Limiting the condition that a benefit "only" has to be approximately cardinally scaled is based on the following consideration: A scale used to measure benefit does not have to be cardinally scaled across its entire range. It is sufficient if it fulfils the criterion of being cardinally scaled across the range relevant for the definition of the patient-relevant added benefit. For instance, different measurement instruments often show so-called floor or ceiling effects at the margins of their value ranges, yet are cardinally scaled across the remaining range [77,237,581].

No specific approach to determine the valuation of benefit on a cardinal scale is recommended here, as each therapeutic area can offer different options that fulfil the requirement of assessing benefit on a cardinal scale.

4.3.2 Outcomes

The benefit can be presented on the vertical axis of the efficiency frontier by means of individual or aggregated patient-relevant outcomes (see Section 3.1.1 for the definition of patient-relevant medical benefit or harm). If several patient-relevant outcomes are presented next to each other, a separate efficiency frontier is created for each patient-relevant outcome. Alternatively, the benefit is aggregated into a single measure of overall benefit, which is subsequently plotted in an efficiency frontier. In a very general definition, a measure of overall benefit is an aggregation of the assessment of benefit and harm into one dimension, whereby different patient-relevant outcomes are summarized into a single measure. It can be considered both in the benefit assessment and in the HEE. The requirements presented in this chapter for the determination of a measure of overall benefit also apply if it is used within the framework of the benefit assessment.

4.3.3 Measure of overall benefit

On an international level, different measures exist to express or determine the overall benefit. These include the QALY and the disability-adjusted life year (DALY). Other measures such as the saved young life equivalent [529] or healthy years equivalent (HYE) [264] were introduced with the objective of correcting weaknesses in the QALY, the most widely distributed instrument.

In this context, depending on the methodological approach or economic theory, the terms "preferences", "utilities" and "values" are used in the scientific literature [200]. We refer to the further debate of the terms and relevance of measurement instruments in relation to the issue of

a welfarist versus an extra-welfarist framework [90], but do not discuss this issue further here. Following SGB V, the following text speaks of weights by means of which individual patient-relevant outcomes can be transferred into a measure of overall benefit.

If the G-BA specifies the measure of overall benefit for an HEE according to §35b (1) Sentence 2 SGB V (see Section 4.9), a respective instrument and, if applicable, the measurement methods specified for this purpose or an already specified weighting of outcomes are used following the requirements of the commission. The results should be made available to the decision maker together with the weighting of outcomes. The option hereby arises for the decision maker to negotiate a reimbursement price weighted by means of several added benefit-based reimbursement prices.

A) QALY as a measure of overall benefit

To calculate QALYs, weights for health states are determined. In this context respondents balance how they perceive or value these health states. The result is then an index score for each health state. Under integration of the duration of the corresponding health states, these weights, largely referred to as utilities (or utility values), can be transformed into QALYs. The determination and calculation of utility values is, for example, presented in Puhan et al. [569], Lipscomb et al. [467], and Tierney et al. [707].

The Institute does not rule out the possibility of using QALYs in HEEs as a measure of overall benefit. QALYs should only be used if the incorporated utility values on the health states are determined in affected persons who currently or in the past experienced these health states. The data on the existing health states for which the utility value is determined should have been collected from participants of clinical studies. If generic index instruments are used, a scale validated in Germany must be used for the determination of the utility value. The use of QALYs, as well as their determination and conversion into a German scale, must in each case be presented in a comprehensible manner and justified. Apart from that, all usual standards for the respective procedures and instruments apply: i.e. evidence of objectivity, reliability, validity, and responsiveness must be available. Parallel to the use of a generic instrument, disease-specific instruments to determine quality of life in clinical studies should be applied. The mapping of disease-specific to generic instruments is therefore discouraged.

In view of the ongoing discussion on the advantages and disadvantages of different instruments, particularly the multi-attribute utility instruments (MAUI), with which quality of life, subjective well-being or utility values can be (or are supposed to be) determined or depicted, one has to say that no general recommendation can be issued. The choice of instrument depends on which of these 3 concepts is to be the most prominent one and which dimensions of quality of life are preferably to be determined [579].

There is no resumption here to the scientific debate about the ethical and methodological problems of the QALY concept itself and their solution or a linked willingness-to-pay threshold

in an HEE, nor of the use of the QALY for the pure weighing of benefit and harm. In this context we refer to a number of publications [172,192,193,322,467,483,502,530,732].

B) Determination of preferences to establish a measure of overall benefit

If a measure of overall benefit for the comparison of interventions is to be determined, in addition to the disease-spanning measures named above, procedures for multi-criteria decision-making or determining preferences can be applied. For outcomes weighted by means of these procedures, all requirements according to SGB V and the Regulation for Early Benefit Assessment of New Pharmaceuticals (ANV[23]) apply. Surrogates can only be used if validity is proven. In the area of health care, the analytic hierarchy process (AHP) and the conjoint analysis (CA) have largely established themselves as methods for multi-criteria decision-making or determining preferences [81,137,365,489,599]. In relation to a specific therapeutic indication, the Institute can thus resort to these procedures to generate a measure of overall benefit. However, there are still unsolved methodological problems in the use of these procedures, so that currently it is not planned to use them routinely.

For the AHP [190,191] a problem in decision-making is broken down into so-called criteria. These are then arranged in a hierarchy. For example, a drug can be assessed by means of the criteria “mortality”, “morbidity”, and “quality of life”. The criteria can be broken down into further subcriteria that can correspond to outcomes [365]. Participants in the AHP then respond to questions about the criteria in a binary way, i.e. on a specified scale they choose how much more a certain criterion means to them than another. By means of a procedure for matrix multiplication [601,602,604] the weights for the criteria and subcriteria can be determined via a so-called “right eigenvector”; these weights must add up to 1. A further development of the method, the analytic network process (ANP), also allows to weight criteria that are dependent of each other [600,603].

The CA belongs to the group of stated-preference techniques [81]. A decision is broken down into so-called attributes that can correspond to outcomes. For each attribute levels are specified. For a discrete choice experiment (DCE = choice-based CA), the choice alternatives (stimuli) are compiled from the attributes with different levels. The respondents are then confronted with a set of (theoretical) scenarios (choice scenario = choice set) consisting of at least 2 stimuli. On the basis of the choice of scenarios, coefficients for the levels of the attributes are then determined in a regression model. The influence of the attributes on the decision can be presented by subsequently forming weights for the attributes. These weights can in turn be standardized to 1.

In its development, the AHP was targeted towards decision-making in the event of opposing aims in committees, for example, the management of a company, and the CA was targeted towards determining preferences to predict purchasing decisions and enable product adaption. Meanwhile, both procedures play a role in the identification and prioritization of patient-

[23] Arzneimittel-Nutzenbewertungsverordnung, AM-NutzenV

relevant outcomes, for example, before the planning of a study, and in the determination of the net benefit (measure of overall benefit) of interventions [155,515].

A clear allocation with regard to which procedure should be preferred in which situation can thus hardly be inferred. An AHP seems to be more suitable if a decision is to be made in a closed group [366]. In contrast, one would conduct a CA if one also wanted to consider compensation for lost benefit if an intervention is not reimbursed. Incidentally, it is also possible to calculate QALYs by means of CA [253,298]. However, when choosing either procedure the following criteria should be used: For the CA a maximum of 6 to 7 attributes can be included; no such limit applies to the AHP. Furthermore, the AHP seems to require lower cognitive effort from the respondents, which, depending on the therapeutic indication, could be considered. These evaluations can currently only partly be based on empirical data so that an evidence-driven choice of either procedure is not currently possible. In addition, there is a need for research on some issues, such as the reliability of both procedures.

The strength and weaknesses of both methods cannot be described in detail here [525]. Comprehensibility with regard to the planning, conduct, analysis, and evaluation of each implementation is thus crucial. For the CA there is a basic list of criteria to ensure high quality, transparency, and reliability of the results of a CA [80]; several of the requirements also apply to the conduct of an AHP.

The following requirements should be fulfilled in detail in the planning, conduct, analysis, and evaluation of the results of surveys using either procedure:

- completeness of the criteria or attributes
- comprehensive documentation of the approach of selecting the respondents and description of the extent to which they are representative (based on sociodemographic and disease-specific factors) for the collective of affected persons

It must be reported not only who participates in the survey, but also how they were recruited. Furthermore, a sample size must be planned. For the CA there are rules of thumb for a sample size estimation [407]. For the AHP there is currently no method for estimating a sample size; however, at least criteria of representativeness can be used here that are also used for other surveys (sample size, method of drawing of the sample, etc.):

- investigation of the population surveyed with regard to homogeneity
- comprehensive documentation of the analysis, together with the handover of raw data, including the verbatim questions
- language, selection and supervision of the implementation, including an assessment of bias through the type of design (a language appropriate for the respondents should be chosen)

- investigation of the consistency and uncertainty of the results by conduct of suitable analyses (e.g. sensitivity analyses).

4.3.4 Data basis

The procedure for the information retrieval for data that are considered on the benefit side in an HEE is described in Sections 8.1 and 8.2. Publications from which conclusions on the measure of overall benefit arise are identified via a focused information retrieval (see Section 8.2.3). Results from surveys on the derivation of weights and utility values can be considered as supplementary information (see Section 4.1.7).

4.3.5 Uncertainty and distribution of benefit data

For estimated effects within the framework of a benefit assessment, confidence intervals or credible intervals (if Bayesian methods are chosen, see Sections 9.3.2 and 9.3.8) can generally be calculated that indicate the precision or uncertainty of the point estimates. Appropriate assumptions should be made for the further investigation of uncertainty, as many effects are not normally distributed.

Estimates from indirect comparisons (see Section 9.3.8) are more subject to uncertainty than estimates from direct comparisons; this is pointed out in the assessment of uncertainty. For estimates from indirect comparisons that, for example, deviate from each other due to different assumptions on a-priori distributions, scenario analyses are potentially performed.

Also in particular for the measure of overall benefit, the investigations of uncertainty (sensitivity analyses) stipulated in Section 4.7 must be conducted.

4.4 Costs

4.4.1 Perspective and costs to be considered

Depending on the commission, the following perspectives can be considered: the (pure) SHI perspective, the SHI insurant perspective, the social insurance perspective or the perspective of individual social insurance branches, as well as the societal perspective. In the following text the relevant costs to be considered are distinguished according to perspectives.

According to the (pure) SHI perspective all direct reimbursable costs and transfer payments (e.g. sickness allowance) are considered. Furthermore, insofar as relevant for the HEE, the proportions can be considered of contributions to pension insurance, long-term care insurance, and unemployment insurance that the SHI must bear in the case of a disease after 6 weeks of incapacity for work, as well as losses in contributions (during the payment of sickness allowance).

In the SHI insurant perspective, in addition to the direct reimbursable costs, insurants' own non-reimbursable co-payments need to be considered (see Section 4.4.2). In contrast, sickness allowance is not calculated, as the payments are merely redistributed from the SHI to the

insurants, so that no additional costs for the community of insurants are incurred [598]. Likewise, losses of contributions for the SHI due to sickness are not considered.

Table 8: Perspective and relevant costs to be considered[24]

Cost category / Perspective	Direct medical costs		Direct non-medical costs		Indirect costs	Transfer payments
	Reimbursable	Non-reimbursable	Reimbursable	Non-reimbursable	-	-
Society	Yes	Yes	Yes	Yes	Yes	No
Social insurance	Yes	No	Yes	No	No	Yes
Community of SHI insurants	Yes	Yes	Yes	Yes	No	No
SHI	Yes	No	Yes	No	No	Yes
SHI: statutory health insurance						

In contrast to the SHI insurant perspective, in the social insurance perspective or that of individual social insurance branches, no co-payments of insurants are calculated. Disease-related, reimbursable expenses including transfer payments are considered.

In the societal perspective, cost components are considered independently of who bears them and who is affected by the effects of an intervention. In general, costs should be considered that are incurred by all social insurance branches and other affected parties (see Table 8). Time expenditure of patients (and/or potentially their relatives) representing loss of working time is not considered once again as time expenditure. Together with the consideration of productivity losses this would lead to double counting. Likewise, transfer payments and SHI-funded contributions to social insurance branches are not considered, as they are merely redistributed and no additional costs are incurred from an economic point of view [598].

In general, when determining costs it should be evaluated in each perspective whether these costs and, if applicable, cost savings, are relevant for the interventions, therapeutic areas, and patient groups investigated.

4.4.2 Distinction of costs

A) Direct costs

Direct medical costs refer to the resource use in the current and future provision of health care services. They are further divided into direct medical and direct non-medical costs. Direct medical costs are understood to be resource use arising from the provision of health care in the health care sector. They include costs, for example, for hospital stays, outpatient visits, drugs,

[24] Depending on the perspective adopted, the content of the respective cost category can differ. In a narrower interpretation of the community of SHI insurants, co-payments, for example, are considered, but no further expenditure of the insurants. This is specified in the G-BA's commissions.

and medical remedies and aids. Direct non-medical costs comprise resources supporting the provision of health care services in the health care sector, for example, travel costs to clinics where medical interventions are performed or the evaluated disease-related time expenditure of affected patients and their care-providing relatives

Reimbursable costs comprise expenditure for health care services funded by the SHI or other social insurance branches. Non-reimbursable medical costs are services directly borne by the insurants, such as co-payments for drugs, medical remedies and aids, and outpatient visits. Non-reimbursable non-medical costs are, for example, disease-related net losses of income[25] (e.g. financial losses of patients receiving sickness allowance below their net income) or the time expenditure of affected patients and relatives.

Most empirical studies do not consider the effects on the leisure time of affected patients and relatives. In this respect the Institute does not regularly consider the time expenditure of these persons in the societal perspective. In case representative and valid information sources on time expenditure are nevertheless available, this expenditure can be considered in sensitivity analyses from the societal perspective. The quality of life of relatives is generally not considered on the benefit side. If their losses of leisure time are investigated, they should also be assessed on the cost side [89,406,540,743].

B) Indirect costs

Indirect costs refer to productivity losses in the event of incapacity for work, occupational invalidity (in the event of long-term disease or disability), and premature death.

The Institute primarily considers productivity losses on the cost side. This is also largely recommended by the literature [91,92,120,200,406,639,640]. To avoid double counting, productivity losses due to premature death (mortality costs) should not be recorded on the cost side if mortality is already considered on the benefit side. Mortality costs are only represented on the cost side in those cases in which the outcome investigated does not refer to mortality or survival time. Costs for society (losses of taxes and contributions to social insurance) are always represented on the cost side [406,639,640].

On an international level it is being discussed whether unpaid work (e.g. housework) should also be taken into account in an HEE. As a rule, this is currently not considered by the Institute.

[25] Strictly speaking the disease-related losses of net income refer to the difference between the net income of healthy persons and that of sick persons, taking into account co-payments for healthcare services to treat the disease. However, within the framework of the SHI insurant perspective, co-payments are not considered as reimbursable costs, so that the net losses of income can be determined from the difference between the sickness allowance paid and the net income of a healthy person.

C) Transfer payments

Transfer payments can be considered, insofar as relevant for the HEE. Generally, transfer payments should not be considered if payments are only redistributed and thus no additional costs are incurred for the perspective selected.

D) Intangible costs

Intangible costs are experiences not directly calculable as resource use or evaluable in monetary units, such as pain or anxiety on the part of the patients treated. Following international health economic standards they should be reported on the benefit side, insofar as data on these details are available.

E) Future costs

Furthermore, the health economic literature often proposes a distinction between intervention-associated and non-intervention-associated (future) costs. Intervention-associated costs are, for example, costs incurred for drugs or check-ups after a heart attack, whereas non-intervention-associated costs would be, for example, treatment costs for cancer occurring later, where treatment has no connection to that for the heart attack.

The consideration of non-intervention-associated costs is the subject of controversial debate [89,200,265,476]. Intervention and non-intervention-associated costs are distinguished from each other depending on the commission. If the extension of life is relevant for the HEE, in the base case the intervention-associated future costs are considered (both for given life expectancy and for life years gained). Non-intervention-associated future costs can be considered in separate sensitivity analyses (not for given life expectancy, as this is identical for all strategies, but for life years gained).

F) Investment and implementation costs

If one-off costs to finance the provision or implementation of health care services arise explicitly for the SHI or the community of SHI insurants, the investment and implementation costs should be appropriately considered. This should be investigated via sensitivity analyses.

4.4.3 Steps for cost estimation

In principle, costs should be determined as precisely as possible. Methods and sources used, as well as results, should be described for the individual steps of cost estimation. The estimation of the costs considered in the model usually follows a 4-step process:

- identification of resources
- quantification of resources
- assessment of resources and
- calculation of the costs considered in the model according to health states and, if applicable, cycles

A) Identification of resources

Within the framework of the identification of resources the health care services used for treating the disease must be determined (see Section 4.1.5). The information should preferably be up to date and can be obtained from the sources described in Section 4.4.4.

B) Quantification of resources

The frequency of use, the proportion of the relevant patient populations using each service, and the duration of the service must be determined. Costs for services that are used very infrequently and/or have only a slight impact on the results should be described, but are not necessarily considered in the calculation [200].

Both a micro- or macro(gross)-costing approach [698,699] can be applied and combined to quantify resource use. The degree of precision of quantification is determined, among other things, by the reimbursement system and the corresponding degree of aggregation of the services.

Both approaches can be applied as a bottom-up or top-down approach [629,698,699] if either the resources used are measured on the basis of the individual patients or an (average) distribution to patients is performed on the basis of highly aggregated data (expenditure for a disease).

C) Evaluation of resources

SHI insurant perspective

In general, regulated and negotiated prices (i.e. prices that have not been exclusively developed via market mechanisms) determine expenditure and represent the opportunity costs of the community of SHI insurants. As described before, the reimbursement system determines the maximum degree of precision in the determination of expenditure of reimbursable costs. For instance, from the SHI insurant perspective, diagnosis-related groups (DRGs, i.e. reimbursement through case fees) and the Uniform Value Scale[26] represent the best-possible evaluation for the inpatient and outpatient sector, respectively.

In the cost estimation for drugs, one distinguishes between the inpatient and outpatient sector. In the inpatient sector, drugs are normally part of the corresponding lump sum reimbursement. If additional fees are negotiated for relevant drugs or these are reimbursed via "new examination and treatment methods"[27], the corresponding costs should be determined and considered in the HEE. In the outpatient sector, at first the pharmacy retail prices are used as a basis for price calculation. If reference prices are available, these must be provided and are reduced by pharmacy and manufacturer discounts. Discounts that were negotiated by a single SHI fund or a group of funds and thus subject to confidentiality are not depicted in the HEE. As a general

[26] Einheitlicher Bewertungsmaßstab

[27] Neue Untersuchungs- und Behandlungsmethoden, NUB

rule, following the principle of efficiency the most economical representative of a drug or drug class is selected. Relevant price changes over time must be considered.

Non-reimbursable costs are partly regulated, so that here one can draw upon the corresponding standardization in the evaluation of resources (e.g. co-payment regulations in the inpatient sector and for drugs). These costs are presented separately in the SHI insurant perspective.

Specific features of further perspectives

Only aggregated data may be available in the social insurance perspective, depending on the insurance branch. In this case the resources should be assessed by means of a top-down approach on the basis of the respective statistics.

When calculating costs from the societal perspective, theoretically one should consider that the societal opportunity costs normally differ from the administrative prices, as these prices only represent the perspective of the payer. For instance, case fees do not include costs for the building of hospitals; from a societal perspective, these costs would need to be allocated to each case fee. The Institute is aware of this theoretical discussion. However, it follows international standards of other HTA organizations, which also use administrative prices in the societal perspective, as a different approach (due to missing data, e.g. on the actual costs that would need to be allocated to case fees for the building of hospitals) would be subject to great uncertainty. It is usually international practice in HEE only to additionally investigate indirect costs. If the time expenditure of affected persons or relatives is considered in the cost estimation, this is evaluated with the net wage.

Evaluation of indirect costs

For productivity losses, in the base case the Institute considers the friction cost approach [295,437], as the human capital approach is based on some unrealistic assumptions (particularly full employment on the labour market). This estimation can be compared with the human capital approach in sensitivity analyses.

In the HEE the evaluation of indirect costs is based on individual labour costs (i.e. gross wage rate and non-wage labour costs – in Germany, employer contributions to social insurance) or the average labour costs. The calculation of the average labour costs per working day is based on the weighted average labour costs of people employed full-time and part-time in Germany. Approximatively, the “employee remuneration in Germany per year” divided by the “number of employees x 365” can be used (whereby Sundays and public holidays must be considered in the work incapacity days). Applying this approach to self-employed people should be discussed [290]. The friction costs are assumed as being 80% of the wage costs (as in the Netherlands [437]). The friction period is, insofar as no current data are available, set at 82 days; this corresponds to the average period in Germany for the year 2016 [373] within which a position can be filled. If the human capital approach is to be investigated in a sensitivity analysis, the future productivity losses are calculated on the basis of the average age of patients up to attainment of the standard retirement age.

D) Presentation of the costs considered in the model according to states or cycles

Before the costs can be fed into the model they must be available as average costs per patient according to health states and, depending on the model, also according to cycles.

Depending on the therapeutic indication, intervention, outcomes, and model, no direct information on the costs of the respective health states in the model is possibly available. On the basis of assumptions from further sources (see Section 4.4.4), the average costs of an intervention per patient and cost category (service areas and indirect costs) for the observation period can then be distributed to the different health states and cycles of the model.

For absorbing states in a Markov model it may be necessary to calculate transition costs that are incurred only once in the transition to this health state. This is then to be recommended if it is to be assumed that the costs in this state are considerably higher in the first cycle than in the subsequent cycles.

4.4.4 Data basis

Costs to be fed into the model must, as described above, be calculated for the different health states and, if applicable, for cycles of a model. The procedure for data collection and analysis, as well as all calculations and results, should be presented in a transparent manner.

A focused information retrieval (see Section 8.2.3) is conducted to retrieve publications and analyses on the identification and quantification of resources.

If current analyses cannot be obtained from the literature, those applying the model should preferably perform their own analyses. In this context, secondary data in the form of analysed SHI routine data based on a representative sample are the data source of first choice (see Section 4.1.7).

Guidelines or results from expert surveys can be used as supplementary information if routine data do not sufficiently depict the provision of health care in all states of the model (see Section 4.1.7). Expert surveys are an option only if data cannot be obtained from more representative sources or if these data do not fully cover the level of detail required in the health states (see also Section 4.1.7).

To determine prices, by means of exploratory literature searches the Institute uses the respective relevant prices regulated or negotiated, for example, from the database of the Information Service on Drug Specialities[28], the Uniform Value Scale, the DRG catalogue or from the statistics of the Pension Insurance or the Federal Statistical Office.

Due to system differences, the transferability of care pathways and cost data from other health care systems is rarely given and is only possible under very strict preconditions [458,654]. The

[28] Informationsstelle für Arzneispezialitäten, IFA

transferability of cost data from the following countries is not excluded as a matter of principle, as their inpatient and outpatient health care sectors are similar to those of the German system: Austria, Switzerland, the Netherlands, Belgium, and France. However, the use of data from these countries must in each case be justified and discussed. Cost data from other countries should not be used in an HEE.

4.4.5 Uncertainty and distribution of cost data

The uncertainty in cost data should be addressed in an adequate manner. Cost data are inherently continuous, positive, without an upper limit and generally not normally distributed, but skewed to the right [36].

4.4.6 Adjustment for inflation and discounting

A) Adjustment for inflation

If cost data originate from different time periods, they must be adjusted for inflation. The Harmonised Index of Consumer Prices (HICP) of the Federal Statistical Office should be used as the source for annual inflation [675]. Further price increase rates for individual areas of health care (e.g. drugs) can be considered from other sources within the framework of a sensitivity analysis.

B) Discounting

If costs and benefits are incurred in periods lasting longer than a year, in the base case they are discounted after the first year with an identical constant rate of 3% to the current period [40,116,166,200,468]. Likewise, identical constant rates of 0 and 5% should be used in sensitivity analyses; any deviations must be justified.

4.5 Epidemiological data

4.5.1 Data

Current epidemiological data are indispensable for an HEE. Besides being used to estimate disease burden, data on the prevalence and incidence in Germany are also used to quantify changes in the SHI budget in a budget impact analysis. Statements are therefore required on whether changes in incidence, prevalence or mortality are to be expected within the next 5 years. Furthermore, data on mortality are important in order to illustrate disease-related mortality and so-called background mortality.

The basic probabilities for events play a special role in modelling. In a model, details on the outcome-related event frequencies or probabilities are required for each outcome, which are considered as baseline values in the decision-analytic model.

4.5.2 Data basis

If available and obtainable in an appropriate form (e.g. suitable age groups), public data collections of epidemiological data (e.g. from the Robert Koch Institute) should be primarily

considered due to their high methodological consistency. Furthermore, epidemiological data can be obtained from secondary data such as SHI routine data as well as registry data (see Section 4.1.7). In this context, registry data take a special position. Independently of the assessment of the quality of a registry, these data are often related only to a specific region. Their applicability must therefore be evaluated. Results from expert surveys can be considered as supplementary information.

If no epidemiological data from Germany are available, a focused information retrieval (see Section 8.2.3) is conducted. If this identifies scientific publications in which epidemiological data were determined, these data can potentially be used directly. Usability must be clarified in the individual case, as the studies often use approaches that are methodologically different. Cohort studies or sufficiently large and representative samples are to be preferred. The methodological quality of the underlying study can, among other things, be assessed by means of the requirements of good epidemiological practice.

4.5.3 Uncertainty and distribution of epidemiological data

The uncertainty in epidemiological data should be addressed in an adequate manner. In particular the uncertainty of data on the baseline risk and on mortality must be adequately considered both in the sensitivity analyses and in the distributions

4.6 Presentation of results as an efficiency frontier

An efficiency frontier is drawn on the basis of the economic evaluation of interventions within a therapeutic area. It is generated from the most efficient interventions of the available comparators and can serve to infer recommendations on decisions for the intervention(s) under assessment. It can provide information on the negotiation of reimbursement prices without recurring to a threshold for the willingness-to-pay, for which there is currently no consent in Germany.

4.6.1 Definition

The efficiency frontier graphically compares the outcome-related benefit of available interventions within a therapeutic area with the net costs of these interventions. In this context, if required, the benefit is transferred into an approximately cardinally scaled measure.[29] Those interventions that are most efficient in respect of benefits and costs form the efficiency frontier.

4.6.2 Course of the procedure

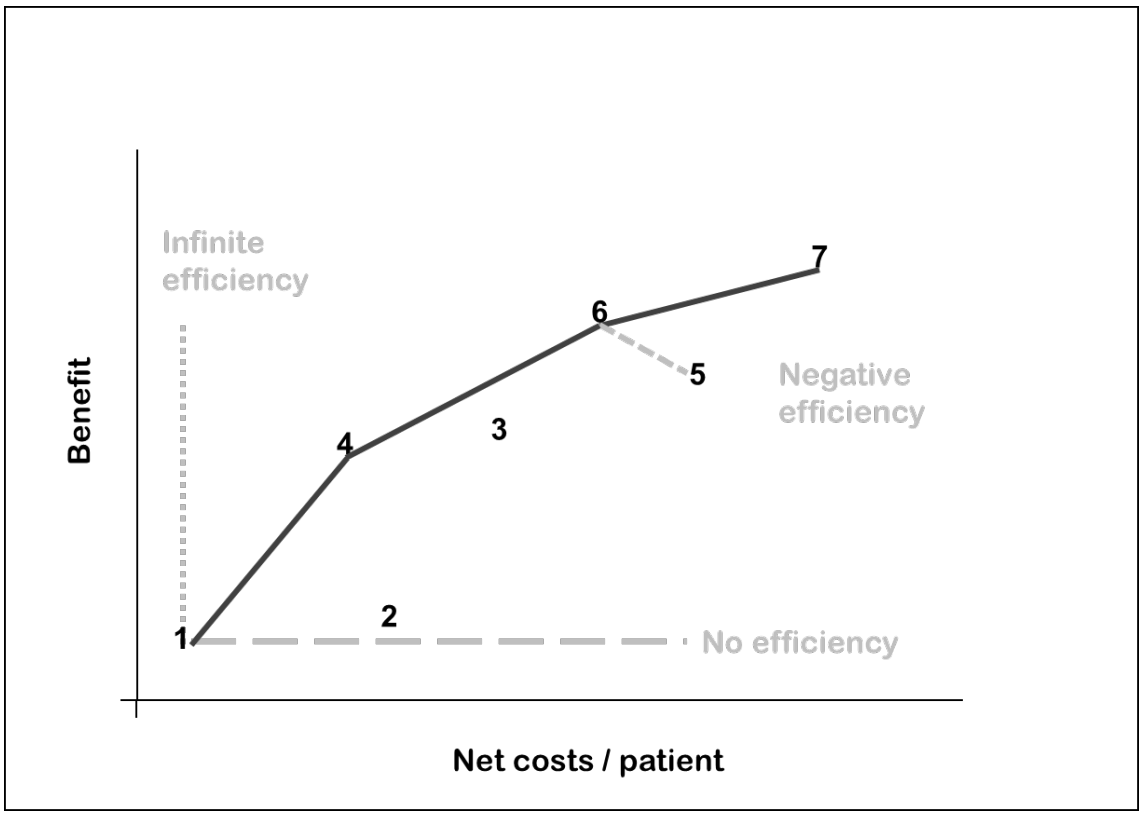
In the procedure it must be distinguished between the new intervention(s) under assessment and the interventions that form the efficiency frontier (comparators). The latter are those

[29] If the patient-relevant added benefit determined in the prior benefit assessment already shows approximately cardinally scaled characteristics, it may be directly transferred into the HEE.

interventions currently used and reimbursed in Germany for the therapeutic area under assessment. Their costs and benefits are determined and depicted graphically.

In the presentation of the efficiency frontier, the interventions with greater efficiency are plotted from left to right. The gradient of the theoretical connecting line between 2 interventions (the line segment) provides the incremental benefit per incremental costs (see Figure 12).

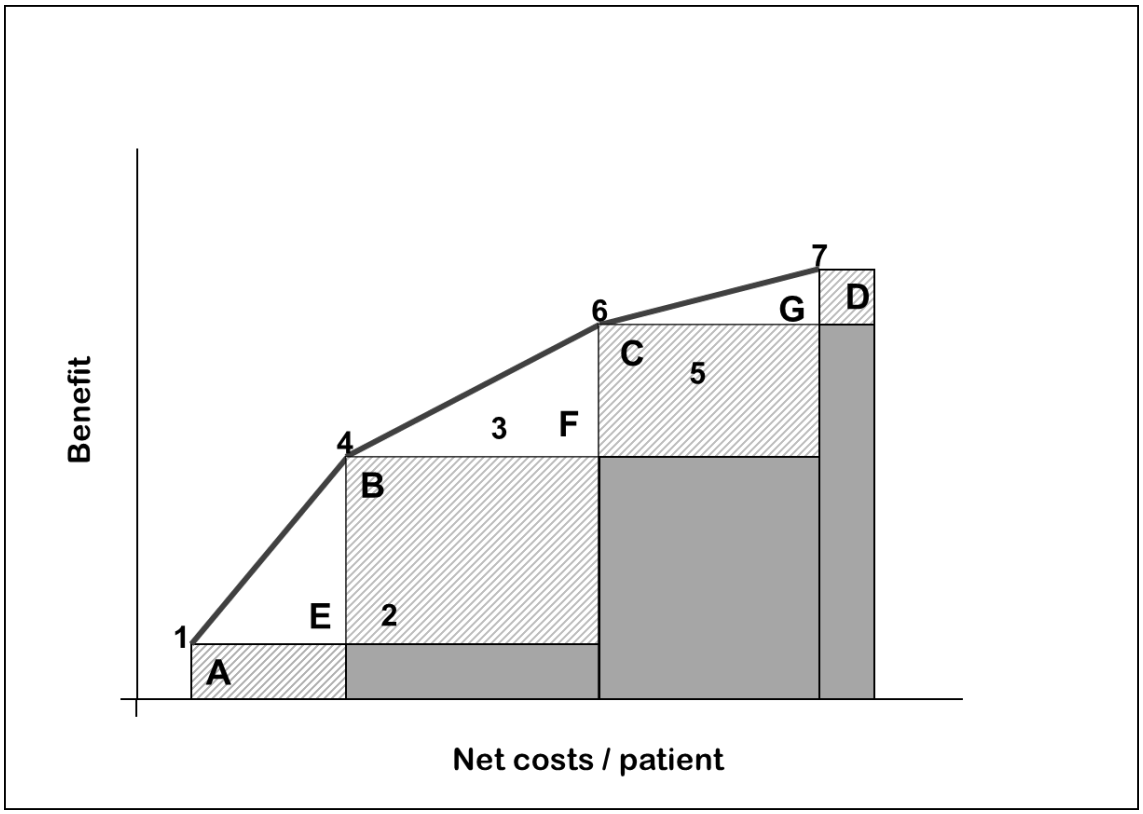
The positions of the interventions, such as Intervention 3 in Figure 12, require further interpretation, as they do not show negative efficiency in comparison with interventions already introduced (e.g. Intervention 4). In Figure 13, the area below the theoretical efficiency frontier is further divided by a series of rectangles (A to D). Each of these rectangles contains all interventions showing negative efficiency (higher costs with lesser benefit) on the theoretical efficiency frontier versus at least one intervention already available in the market. Interventions in these subareas (e.g. Intervention 2 or Intervention 5 in Figure 13) are clearly inefficient. This leaves 3 triangles (E, F and G) in which the interventions are not clearly inefficient. Usually, interventions plotted in these triangles are not part of the efficiency frontier because a theoretical combination of both interventions forming the hypotenuse of the triangle will provide a greater benefit with lower costs (so-called extended dominance).



A horizontal line (gradient angle = 0°) indicates no efficiency, while a vertical line (gradient angle = 90°) indicates infinite efficiency. A positive gradient in ascending order (e.g. between Intervention 6 and Intervention 7) indicates an incremental benefit with higher costs, whereas a negative gradient (e.g. between Intervention 6 and Intervention 5) indicates lesser benefit with higher costs.

Figure 12: Interpretation of the gradient of the theoretical efficiency frontier

Such a combination is not always possible in practice. This would imply that if the price of Intervention 3 is fixed, then the beneficiaries would need to be redistributed to Intervention 4 and Intervention 6 to achieve greater efficiency. This may be clinically undesirable and difficult to justify, since it would lead to those receiving Intervention 4 being in a worse position. The alternative of allowing beneficiaries to switch between both therapies over time is clearly not possible with most surgical interventions, and presumably not for many drug interventions either. Thus, there may be many situations where interventions within the triangular areas constitute part of the practical efficiency frontier. If the criterion of extended dominance is not applied, then this results in a stepped absolute efficiency frontier arising from the connection of the upper segments of the shaded rectangles as opposed to the triangular areas. However, in this context it needs to be considered that the absolute efficiency frontier no longer provides a gradient in the sense of a reciprocal of the willingness-to-pay and thus no threshold values would be determined.



The theoretical efficiency frontier (solid line) joins those interventions that are efficient relative to any other intervention or to their combinations. Interventions in Rectangles A to D (e.g. Intervention 2 or Intervention 5) are clearly inefficient. Intervention 3 is in one of the remaining triangular areas (E to G) and is not clearly inefficient. Theoretically an extended dominance would result from the combination of Intervention 4 and Intervention 6, but this may not be feasible in practice.

Figure 13: Absolute versus extended dominance

4.6.3 Construction of the efficiency frontier

The efficiency frontier is constructed in such a way that it represents the relevant interventions in a given therapeutic area. This involves:

- Full, detailed specification of the therapeutic area of interest. This may include the specific disease, the conditions of treatment (e.g. inpatient care), target population, sequence of therapy (first, second-line therapy, etc.), and the information on whether it is a mono-therapy or combination therapy.
- Positioning of existing therapies on the basis of their benefits and costs.
- Plotting of the interventions on a coordinate system with the benefit on the vertical (y-) axis and the costs on the horizontal (x-) axis.[30] In this context, in accordance with good scientific practice, one should ensure constant scaling (at least per outcome) of the axes.
- Drawing of the efficiency frontier.

When evaluating new interventions, their health effects and costs in the therapeutic area in question are then additionally presented.

A) Vertical axis

- Benefit and harm are plotted on a vertical axis. In this context, one should observe a positive value range, so that the efficiency frontier depicts the increased benefit or decreased harm (if applicable, e.g. multiplication with "−1" may be required or conversion to the complementary event "1−harm").
- Benefit or harm is presented by means of patient-relevant outcomes that must be operationalized in an appropriate manner (e.g. quality-of-life scores).
- Benefit or harm is transferred onto the vertical axis. This transfer can be performed with inclusion of modelling.

B) Horizontal axis

- The total net costs per patient are plotted on the horizontal axis.
- As a rule the costs are calculated from the SHI insurant perspective. Depending on the commission, they may contain additional costs arising from extended perspectives, (e.g. social insurance perspective, societal perspective).
- The costs currently to be expected are used as costs.

In order to estimate the costs of each intervention and plot them on the coordinate system of the efficiency frontier, several conditions must be met. The costs should correspond to those that

[30] This could also be presented as a table. However, the relationships would not be so graphically visible.

would be incurred in current practice. The total net cost per patient must be plotted on the efficiency frontier.

To determine the cost-effectiveness ratio of (new) interventions with more benefit and more costs than the comparators, the last segment of the efficiency frontier is extended (see Section 4.1.9 as well as Figure 11 and Figure 14).

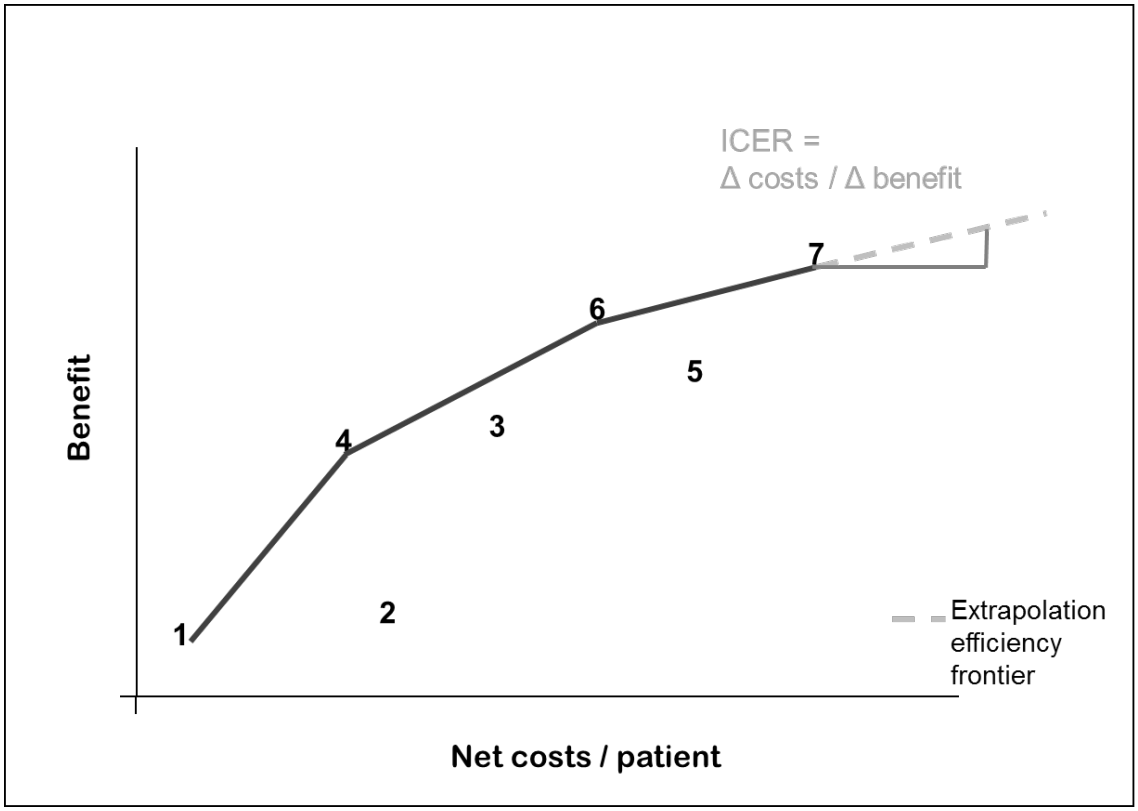
Depending on the number of outcomes taken from the benefit assessment previously conducted, several efficiency frontiers can be derived and presented.[31] If outcome weighting was performed, this is also presented. If a measure of overall benefit was specified, this is to be regarded as the primary result.

C) Definition of the origin of the coordinate system

The point of no intervention (i.e. the natural course) also requires an assessment. Although it could possibly be regarded to be the coordinate origin (zero benefit and zero costs), this is rarely appropriate, as the non-conduct of an intervention may still produce costs and health effects, for example, due to the untreated disease, monitoring, etc. Data on the natural course should therefore also be collected. In this context a common assumption is that the intervention with placebo most likely corresponds to the natural course. This should be assessed in relation to each commission.

If the origin of the efficiency frontier does not correspond to the zero point, the efficiency frontiers (at least per outcome) must be plotted in equally scaled coordinate systems. The intervention that lies the furthest down and to the left will generally become the origin of the efficiency frontier (see Figure 14). For reasons of comparability of the presentation of different efficiency frontiers, a shifting of the zero point (of the coordinate system) should be rejected.

[31] This also refers to the separate presentation of divergent aspects of harm in distinction from the patient-relevant added benefit.



The efficiency frontier starts in a different origin from the zero point of the coordinate system. The extension shows the incremental cost-effectiveness ratio (ICER) at which a (new) intervention with more benefit and more costs than the comparators is measured.

Figure 14: Presentation of the efficiency frontier

4.6.4 Special constellations

There are 2 special constellations in which, despite complete information, a recommendation for a new intervention cannot be directly inferred on the basis of the efficiency frontier:

1) The last intervention on the efficiency frontier dominates all other interventions and generates the same costs as the reference scenario. The gradient would thus be infinite (see presentation in Figure 12).
2) The last intervention on the efficiency frontier before the introduction of the innovation is more cost-efficient and has more benefit than all comparators, including the origin.

Both cases would result in a new origin, on which in each case the last intervention before the introduction of the innovative intervention would lie.

The budget impact analysis might deliver further data here by depicting the impact on the budget (see Section 4.1.9 and Section 4.8).

4.7 Uncertainty (sensitivity analyses)

The types of uncertainty are presented above (see Section 4.1.8). The uncertainty of many model parameters results from the fact that their value is estimated from samples. This type of uncertainty is often captured by confidence intervals or other statistical approaches for describing variability.

4.7.1 Quantification of uncertainty

For costs, uncertainty may exist regarding assumptions on resource use, for example, on dosage of a drug over time. The model can also be of a stochastic design (i.e., it uses random numbers in the Monte Carlo draws). Different techniques can be applied to restrict this type of uncertainty [454,587,650] .

Uncertainty also arises from the type of potential variability in the model structure described in Section 4.2, which needs to be considered in the investigation. Finally, even input parameters specified a priori, such as the discounting rate, can be varied to depict uncertainty arising from different discounting rates (see Section 4.4.6).

4.7.2 Sensitivity analyses

Parameter uncertainty as well as types of uncertainty that cannot be reduced are quantified. The Institute considers both univariate and multivariate deterministic as well as probabilistic sensitivity analyses (PSAs), and in its work follows the recommendations of the conjoint Modeling Good Research Practices Task Force Working Group of ISPOR and the Society for Medical Decision Making (SMDM) [82].

All analyses performed for this purpose should be fully documented, with minimum and maximum values for the parameters used and underlying assumptions. The following aspects must be specified for PSAs: probability distributions used and their sources, correlations between input parameters, and any structural variants.

Structural sensitivity analyses are performed to investigate the impact of a variation of assumptions in the model structure, for example, the number or type of the model states.

Presentation of the results of the sensitivity analyses

For the deterministic sensitivity analysis, extreme levels of the input parameters should be provided for which the new intervention possibly saves costs or lies above or below the efficiency frontier. For univariate and multivariate analyses the results must be presented in a table and in a tornado diagram in which the levels of the results are displayed as an interval for the corresponding intervals of the input parameters.

For PSAs the proportion of simulations for which cost savings or a position above or below the efficiency frontier arises is provided as a percentage. In the case of PSAs the results are presented as cumulative cost distributions.

4.7.3 Presentation of uncertainty by means of the net health benefit

When presenting results of sensitivity analyses, attention should be paid to the fact that the consideration of parameter uncertainty can on the one hand change the position of several or all interventions forming the efficiency frontier. On the other, the position of the intervention under assessment, which is contrasted with this efficiency frontier, can also change.

The net health benefit (NHB), an established procedure for presenting results from PSAs, [682] can account for this problem, as the NHB is a function both of the added benefit and added costs, and also of the efficiency frontier, and depicts the position of the intervention under assessment as the distance to the shifting efficiency frontier or to the shifting last segment of the efficiency frontier. For this reason, both the base case analyses, as well as the deterministic and probabilistic sensitivity analyses, should be conducted on the basis of the concept of the NHB calculation.

4.8 Budget impact analysis

A BIA is an assessment of the direct financial consequences related to the reimbursement of an intervention in a health care system [712]. In a calculation model for a BIA, the proportion of patients who will potentially receive a new intervention is considered, as well as the dissemination of the intervention in the health care system, including its use in previously untreated patients. In particular, a BIA predicts how a change in the mix of interventions used for a certain disease might in future influence expenditure for a therapeutic area [497].

The purpose of a BIA is not so much to produce exact estimates of the financial consequences of the use of an intervention, but rather to provide a reliable calculation framework that allows the decision maker to understand the possible expenditure effects of a new intervention (or of a change in the usage of existing interventions) [497]. Such a model is necessary, as many of the parameters vary depending on the constellation and are also subject to uncertainty. Thus, the result of the BIA is not a single value for the estimation of expenditure but rather a range resulting from the model.

4.8.1 Perspective in the budget impact analysis

The BIA should be undertaken from the perspective of the SHI or another relevant payer (see also Section 4.4.1). Any expenditure incurred or cost savings achieved outside this perspective are not included.

4.8.2 Time horizon in the budget impact analysis

The BIA should cover the time horizon most relevant to payers in view of their expenditure [497]. Since the impact on expenditure is likely to change over time after the new intervention has been introduced – both because of market adjustment and of long-term effects on the disease in question – this horizon should be estimated and presented for a period of 1 and 3 years [496]. The results must be presented as expenditure and cost savings per year instead of in the form of a single net current value [497]. Thus in this case no discounting of financial flows is allowed

to be performed. If the result is presented as a total amount of costs for 3 years, the costs can be discounted accordingly (see Section 4.4.6).

4.8.3 Scenarios in the budget impact analysis

A BIA compares health care scenarios – each defined by a compilation of interventions – rather than specific individual interventions [497]. At least 2 scenarios must be considered: on the one hand the reference scenario, defined by the current mix of interventions, and on the other, the predicted new mix of interventions.

4.8.4 Population in the budget impact analysis

The size of the insured population likely to take advantage of the new intervention is one of the key factors determining the expected expenditure for the new intervention. The anticipated number of users results from the predicted utilization of the intervention within the target population. Any expected off-label use of the new intervention should not be considered in the primary BIA, but may be considered in sensitivity analyses [542].

When predicting the number of users, both the substitution of existing interventions and induced demand need to be taken into account.

4.8.5 Costs to be considered in the budget impact analysis

The costs (net costs, i.e. adjusted for cost savings, so-called cost-offsets) should be estimated according to the methods described in Section 4.4.

For the BIA, investment and implementation costs are – as far as possible and borne by the SHI – identified and quantified. They should be presented separately and organized according to cost categories, whereby a complete explanation of the method and the sources used for cost estimation must be included.

4.8.6 Presentation of results in the budget impact analysis

The results (in €) should be presented as a value range and not as single point estimates. Furthermore, both the total amount and the proportion related to annual expenditure should be displayed.

4.9 Specific aspects of a health economic evaluation according to §35b SGB V

4.9.1 Legal requirements and course of procedure

Some specific requirements apply for the HEE according to §35b SGB V. By default there are 2 constellations that can lead to an HEE within the framework of the benefit assessment of drugs according to §35a SGB V:

1) If a pharmaceutical company disagrees with the decision by the G-BA that the drug under assessment has no added benefit or does not represent a therapeutic improvement, according to §35a (5a) SGB V, the pharmaceutical company can demand that the G-BA commissions an HEE according to §35b SGB V or to §139a (3) No. 5 SGB V.
2) After a decision by the arbitration board, according to §130b (8) SGB V, both the pharmaceutical company and the SHI umbrella organization[32] can commission an HEE according to §35b SGB V.

If a pharmaceutical company and/or the SHI umbrella organization submit an application to the G-BA for an HEE according to §35b SGB V, further specific aspects arise during the course of the procedure, which are described in Section 2.1.4.

According to §130b (8) Sentence 3 SGB V, an HEE of drugs according to §35b SGB V serves the purpose of negotiating a reimbursement price that is to be negotiated in comparison with (an) appropriate comparator therapy or therapies. According to §35b SGB V, the G-BA specifies the following points in its commission on an HEE:

- appropriate comparator therapy and other drugs and treatment forms with which the drug under assessment is to be compared
- patient groups
- time period
- type of benefit and of costs and
- measure of overall benefit

The basis of the HEE are 1) the results of clinical studies, 2) the results of health services research studies agreed upon with the G-BA or recognized by the G-BA after application by the pharmaceutical company, and 3) evidence provided by the pharmaceutical company (see §35b (1) Sentence 3 SGB V). Moreover, due to the legal situation in Germany (§35b (1) SGB V), as a rule the SHI insurant perspective is adopted. More details are described in the G-BA's Code of Procedure (see Chapter 5, Section 2) [271].

4.9.2 The net health benefit for calculation of added benefit-based reimbursement prices

As explained in Section 4.7.3, the NHB can be used to present uncertainty. On the basis of the expected value of the NHB of the intervention under assessment, an added benefit-based reimbursement price can also be derived via the further calculation of the cost-adjusted (added) benefit of the intervention under assessment [683].

[32] Spitzenverband Bund der Krankenkassen, GKV-Spitzenverband

The incremental NHB is calculated by means of the effect estimate for the benefits and the costs of the respective interventions as well as a threshold value. In this application the threshold value corresponds to the reciprocal of the gradient of the last (and potentially extrapolated) segment of the efficiency frontier for cost-effective interventions (see Figure 15). If the NHB were about zero, then Intervention 8 would lie on the efficiency frontier determined by the gradient ($1/\lambda$) of the last segment of the efficiency frontier, and can also be assessed as cost-effective in comparison with the (per definition cost-effective) interventions forming the efficiency frontier. Accordingly, an added benefit-based reimbursement price is determined by means of the NHB by conversion and calculation of the maximum intervention costs that are necessary to ensure that the NHB is at least zero. The NHB can be estimated practically with the help of the model through iterative calculations.

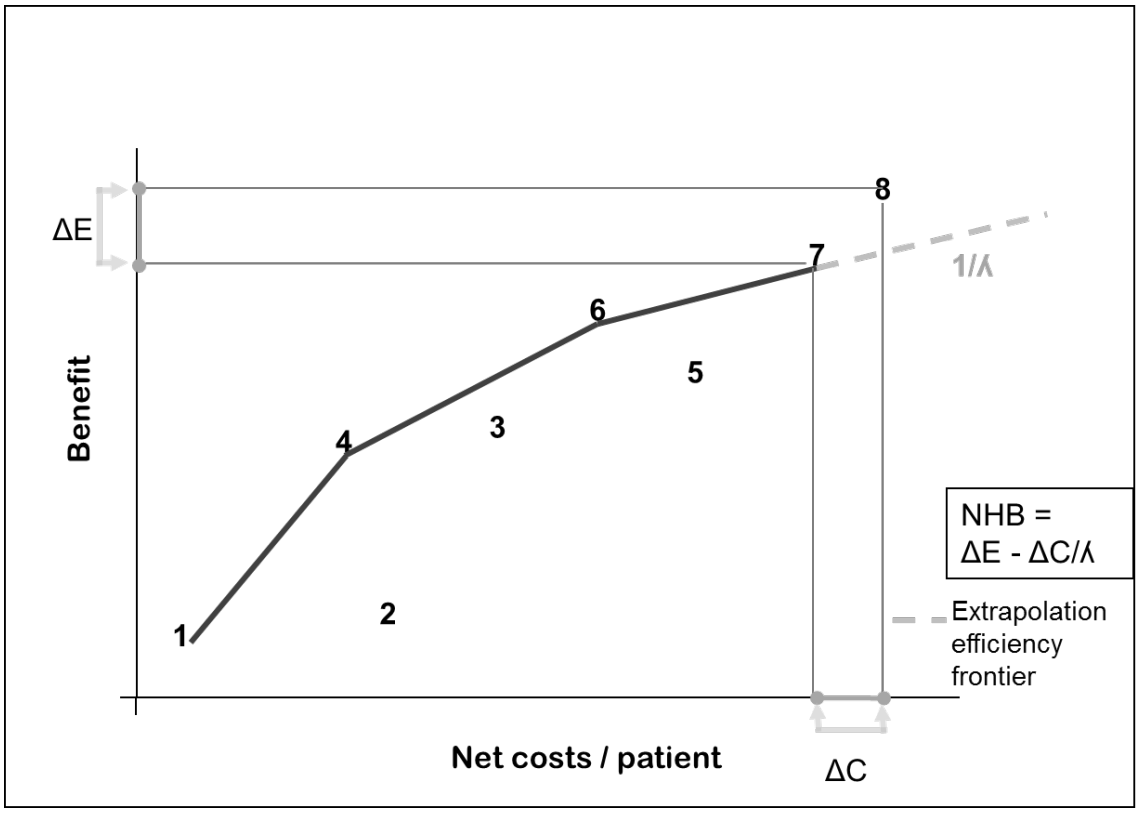


Figure 15: Presentation of an NHB > 0

4.9.3 Sensitivity analyses for the calculation of added-benefit based reimbursement prices

For the added benefit-based reimbursement price, price acceptance curves [242] and/or NHB values can be presented per efficiency frontier (see Section 4.9.2).

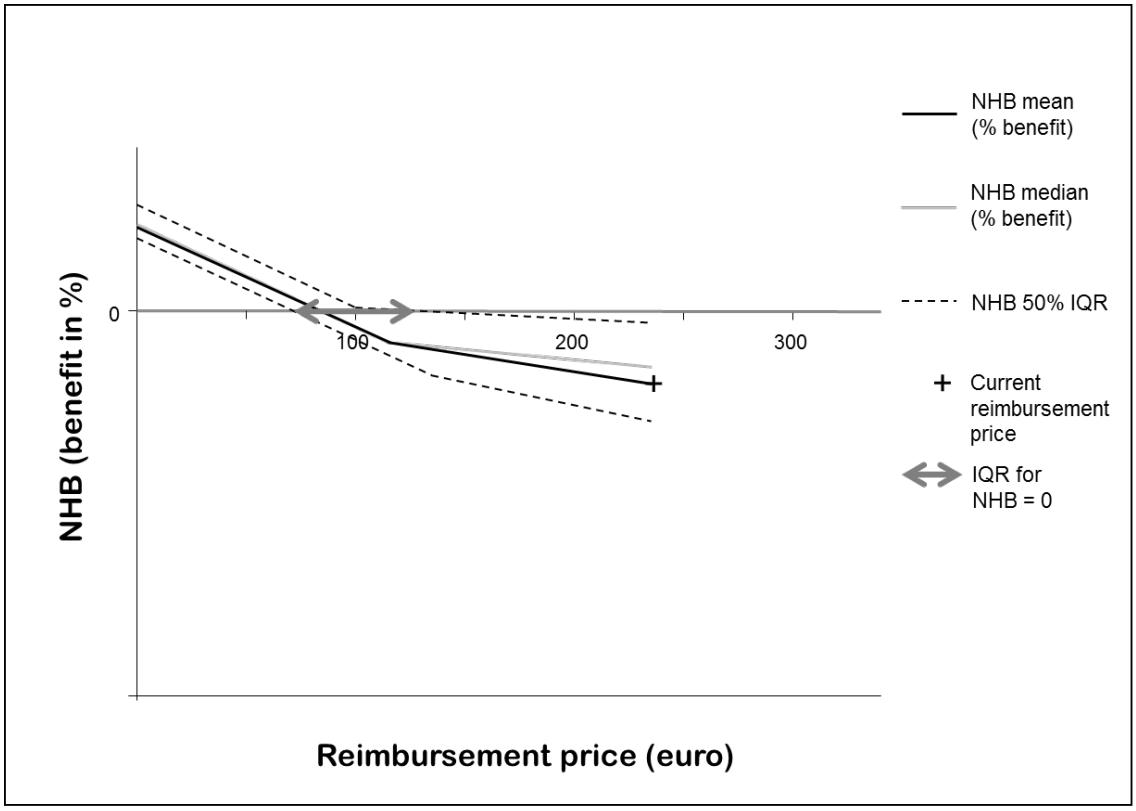
When using the NHB the results of the PSAs should be presented via the calculation and averaging of the respective expected NHB values for the intervention under assessment for a sufficiently large number of runs. In each run both the efficiency frontier and the position of the intervention under assessment relative to the efficiency frontier, and thus the respective

NHB value, can change. From these values, the averaged NHB value of the intervention under assessment, as well as an interquartile range (IQR), can be calculated (see Section 4.9.4). In combination with the IQR, the expected NHB value indicates how large according to expectation the cost-adjusted (added) benefit is for the current added benefit-based reimbursement price, under consideration of the model uncertainty.

4.9.4 Interquartile range as a measure of dispersion for price negotiations

An IQR is provided to give the SHI umbrella organization and the pharmaceutical company a measure of dispersion for the negotiations on the basis of the results of the sensitivity analyses (see Section 4.7). The IQR includes all values of the NHB from the simulations margined by the lower and upper quartile (see Section 4.9.3). This means that the IQR covers those 50% of simulations in the PSAs that lie above the 25% lowest results and below the 25% highest results (see Figure 16). In principle it can also be meaningful to provide other areas of distribution with other measures.

Under consideration of the total uncertainty (implemented through PSAs), the IQR allows room to open possible reimbursement price negotiations within whose margins the uncertainty of the effect estimates and the costs are also considered.



For each possible reimbursement price the solid line indicates the average NHB to be expected (x-axis). At the position where the solid line crosses the x-axis, an added benefit-based reimbursement price can be read off in which the average NHB to be expected is zero, that is, neither positive nor negative.

Figure 16: Interquartile range of possible added benefit-based reimbursement prices (based on PSAs) as a measure of dispersion for price negotiations

5 Analyses of health care

5.1 Evidence searches for guidelines

5.1.1 Background

Clinical practice guidelines are systematically developed normative action and decision aids for service providers as well as patients enabling an appropriate approach to specific health problems. Their aim is to improve patient care [755]. Ideally, their recommendations are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative treatment options [246,291]. In addition to all relevant professional groups involved in the health care provided, guideline groups should also integrate affected persons as well as persons with methodological experience in guideline development.

With the Digital Health Care Act (DVG[33]), it was stipulated that the AWMF can propose clinical practice guidelines to the Federal Ministry of Health for which IQWiG is to support guideline development or updating with evidence searches [3]. An evidence search usually includes the production of several evidence reports.

5.1.2 Evidence reports

The evidence report answers the question as to what evidence exists regarding the effects of a specific intervention compared with a control intervention in a clearly defined population. This research question is called the PICO[34] question. It is addressed based on the methodological requirements of GRADE [634] and conforms to the General Methods. As a result, (quantitative) evidence profiles are generated. In contrast to the benefit assessment described in Chapter 3, in which the effects of an intervention are evaluated on an outcome-related basis and a conclusion is inferred regarding benefit or harm, such a conclusion is not inferred in the evidence reports. This final step is the responsibility of the respective guideline groups within the development of recommendations for action.

Qualitative evidence reports can also be produced with the aim of answering questions about the patient or family perspective, feasibility, or acceptance of this intervention [509]. For this purpose, on the basis of qualitative studies qualitative evidence profiles are generated roughly following the GRADE CERQual[35] instrument [459]. Instead of the PICO scheme, the PICo[36] scheme is used [471].

[33] Digitale-Versorgung-Gesetz

[34] Population, intervention, comparison, outcome

[35] Confidence in the Evidence from Reviews of Qualitative Research

[36] Population, phenomena of interest, context, others / outcome

5.2 Guideline synopses

5.2.1 Background

Guidelines can include recommendations for action in one or more areas of the health care chain (prevention, diagnosis, therapy, rehabilitation and aftercare) for one or more specific health problems. To provide an overview of the most important evidence-based recommendations for the health care of patients with a selected clinical picture across the entire health care chain, guideline synopses summarize the recommendations of national and international guidelines of high methodological quality that were identified in a systematic search. In this way, they help to bundle information on the quality of health care to be aimed for in a health care system [325].

Guideline synopses are particularly suitable to provide an overview of normative health care requirements for selected diseases. Among other things, they serve the G-BA as a basis for developing and updating the requirements for structured treatment programmes for chronically ill people (disease management programmes [DMPs]). These are described under various items in the DMP Requirements Directive (DMP-A-RL[37]) [271,274].

5.2.2 Evidence-based guidelines

Evidence-based guidelines are normally used to answer questions on health care standards within the framework of guideline synopses. Guidelines are referred to as evidence-based if their recommendations are based on a systematic literature search and selection, if their recommendations are generally linked to a grade of recommendation (GoR) and/or level of evidence (LoE), and are linked to citations of the underlying primary and/or secondary literature (modified according to AGREE[38] [8,9]). An evaluation of these formal criteria, but no evaluation of content, is performed for the inclusion of guidelines in the guideline synopses.

5.2.3 Applicability to the German health care system

If national as well as international guidelines are searched for in the production of guideline synopses, it is in principle assumed that guidelines from member states of the OECD are particularly relevant. The OECD was originally established in 1961 as the follow-up organization of the Organization for European Economic Co-operation [541]. Besides a high per-capita income by global standards, these member states have high-performing health care systems. Since 2003 the OECD has been aiming to compare the quality of health care in the different member states via the common reporting of selected quality indicators (Health Care Quality Indicators [HCQI] project [495]).

In principle all guidelines from the OECD member states can be considered. However, the applicability of recommendations from international guidelines can be problematical if they represent specific recommendations that, for instance, are not compatible with the funding principles of the German health care system or with the special features of the SHI system in

[37] DMP-Anforderungen-Richtlinie

[38] Appraisal of Guidelines Research and Evaluation in Europe

Germany with regard to the legal regulations for professional conduct or for the provision of health care services. This is considered in the synopses of the guidelines, where necessary.

5.2.4 Appraisal of methodological guideline quality

An important aspect in the interpretation and appraisal of guideline recommendations within the framework of the guideline synopsis is the appraisal of the methodological quality of the underlying guidelines. No examination of content quality is carried out.

On an international level different instruments are used for the appraisal of methodological guideline quality [655,736]. Special attention is paid to the AGREE instrument [8,482] and its further development (AGREE II instrument) [9,93-95]. It was developed by an international group of researchers and is the most widely used instrument internationally. It is therefore also used in guideline synopses to appraise the methodological quality of the guidelines included.

The AGREE II instrument [9] consists of 23 appraisal criteria (items) assessed by means of a multi-step scale. These items are organized in 6 domains, which are independent of each other; each domain covers a separate dimension of methodological guideline quality:

- Domain 1: scope and purpose
- Domain 2: stakeholder involvement
- Domain 3: rigour of development
- Domain 4: clarity and presentation
- Domain 5: applicability
- Domain 6: editorial independence

While the AGREE instrument [9] specifies the calculation of standardized domain scores for each of the 6 domains, its use within the framework of guideline synopses is limited to Domains 2,3 and 6. This is done with a view to the objective of the guideline synopses according to SGB V and the Rules of Procedure of the G-BA [271] in order to provide an evidence-based basis for updating existing DMPs and developing new ones. The limitation to Domains 2, 3 and 6 is also undertaken by other authors [55].

Each guideline appraisal is performed by 2 reviewers independently of each other. Each standardized domain score is presented in the guideline synopsis. AGREE does not provide any thresholds to distinguish between methodologically strong and methodologically weak guidelines [9]. However, some users of the AGREE II instrument make recommendations for the use of guidelines based on the standardized domain scores, using 2- and 3-level systems. In the 3-level system, guidelines with domain scores below a specific value – but varying according to the user group – are considered weak or not recommended [355]. Following this procedure, guidelines that achieve standardized domain scores < 30% in 1 or more of the 3

domains considered are marked in the guideline synopses. This also applies to results based exclusively on such guidelines.

The results of the AGREE II appraisal are thus not a criterion for the inclusion of guidelines in a guideline synopsis, but marking is used to transparently show whether the evidence-based guidelines included in a guideline synopsis show particular methodological strengths or weaknesses.

5.2.5 Structured processing of recommendations: levels of evidence and grades of recommendation

A guideline recommendation is defined as a proposal for action concerning the clinical decision in a specific situation or for system decisions. The recipients are generally professionals. In guidelines those statements are generally identified as recommendations that are clearly formally indicated as such by the guideline authors.

The authors of evidence-based guidelines use different systems to classify the LoEs or GoRs of their recommendations [29,207,309,445,637].

GoRs provide information on the strength of a recommendation. They are generally based on a weighing of the benefit and harms of a (medical) intervention and on the specific health care context based on an evaluation of the respective evidence. LoEs focus on the internal validity of the underlying studies; in this context, systematic reviews of RCTs usually receive the highest LoE. The systems of evidence classification may attribute a differing relevance within the LoE classification to clinical and epidemiological studies, the characteristics of study conduct, and the respective risk of bias [29,97-99,309,637].

As there is to date no internationally consented standardization of grading systems for evidence and recommendations, the LoEs and GoRs used by the individual guideline developers are generally noted in the guideline synopsis and the corresponding grading systems documented. In order to better compare the different systems of different author groups of guidelines, the classification of GoRs and LoEs for the guideline synopses is simplified by transferring them into a standardized category system. In this context, a distinction is made between “high”, “not high” and “unclear” categories.

In the Institute’s work, the grading system from the procedure of the National Health Care Guideline (NVL[39]) is relevant for the assessment of GoRs [103]; the evidence classification applied by the G-BA is used for the classification of LoEs [271]. A high GoR is assigned if the measure recommended can be assigned to the strength of recommendation “A” (strong recommendation). All other recommendations are assigned to the category “non-high or unclear GoR”. An LoE assigned by the guideline authors is classified as high if the LoE is based on at

[39] Nationale VersorgungsLeitlinie

least one RCT. This corresponds to evidence levels Ia and Ib of the evidence classification used by the G-BA.

If the guideline authors use a classification system according to the GRADE Working Group [305,306,309], the highest evidence level according to GRADE is generally assigned to the category "high LoE". All other LoEs provided by the guideline authors that cannot be assigned to the category "high" are assigned to the category "non-high or unclear LoE".

The category "unclear" is assigned if

- a GoR specified by the guideline group cannot be categorized according to the recommendation grading system of the NVL programme
- an LoE specified by the guideline group cannot be categorized according to the evidence classification of the G-BA or GRADE
- the GoR / LoE specified cannot be clearly assigned to a recommendation or
- no GoR / LoE is specified.

5.2.6 Structured synthesis of information: extraction and analysis of recommendations

The basis for the synthesis of recommendations within the framework of the guideline synopsis are current evidence-based guidelines. In the first step, the recommendations of the guidelines are compared with the content of the currently valid DMP-A-RL. In this context, the recommendations are assigned to the respective statements of the DMP-A-RL (so-called health care aspects).

In the case of existing DMPs, it is checked when assigning the recommendations whether their content is discrepant to the DMP-A-RL. For the further analysis, only those health care aspects are considered that contain recommendations discrepant to the DMP-A-RL.

The recommendations of these health care aspects are assigned to both the evidence and recommendation levels according to Section 5.2.5. The methodological assessment is based on this: Only health care aspects that contain recommendations with at least one high GoR or alternatively only recommendations with an unclear GoR (whereby at least one of these recommendations must have a high LoE) are considered for the development of key statements and are presented in the guideline synopsis. For this purpose, the main content of the recommendations is summarized per health care aspect (key content).

The discrepancy between the health care aspect and the DMP-A-RL is explained briefly and concisely in the results tables. If necessary, these explanations are supplemented by methodological and other scientific information, for example, on relevant details that deviate from health care in Germany or scientific discourses.

In the case of guideline synopses on new DMPs, the procedure is the same, with the exception of the comparison with the DMP-A-RL.

5.3 Minimum volume regulations

5.3.1 Background

The potential correlation between defined volumes of services in (mainly inpatient) facilities and quality has been investigated for more than 40 years [494]. Since 2003, the G-BA has set so-called binding minimum volume standards for hospitals in accordance with §137 (3) Sentence 1 No. 2 SGB V – old version, now §136b (3) Sentence 1 No. 2 SGB V – for certain inpatient elective services: Hospitals may only provide and bill the corresponding services if the competent hospital operators convincingly demonstrate to the regional associations of the health insurance funds that they will at least meet the minimum volume standards in the next year on the basis of the volume of services achieved in the previous year.

These minimum volume regulations are binding for hospitals licensed according to §108 SGB V and specify in which case a hospital site may provide the services for which minimum volumes have been specified [269]. However, some exceptional rules apply. For example, emergencies, as a matter of principle, remain unaffected by the minimum volume regulation. Or the authorities of the federal states ("Länder") responsible for hospital planning can determine exceptional rules for those services where the application of the minimum volume regulation could endanger guaranteeing the provision of area-wide health care for the population.

In order to specify a new minimum volume or to review an existing one, the G-BA can commission IQWiG with the scientific assessment of the correlation between volume of services and quality for a specific medical procedure (§136b (1) Sentence 1 No. 2 SGB V and Chapter 8 §16 (5) Sentence 1 No. 1 of the Rules of Procedure of the G-BA [271]).

5.3.2 Information basis and assessment

The investigation of the correlation between the volume of services and the quality of the treatment outcome is based on appropriate observational studies or controlled intervention studies. Results for different target variables are considered. These may relate to mortality, morbidity, and health-related quality of life, including activities of daily living and dependence on the help of others.

Since the quality of the treatment outcome of a medical intervention can be influenced by numerous individual risk factors of the patients, as well as by the quality of the intervention itself, only those observational studies are included in which relevant confounding factors were controlled for (risk adjustment).

The informative value of the results of observational studies is assessed on the basis of quality criteria developed specifically for studies evaluating volume-outcome relationships

[52,375,376,747]. Various issues are examined in this context (data sources used, adequacy of the statistical models, appropriate risk adjustment and completeness of reporting). On the basis of this qualitative assessment, a quality classification of the observational studies into studies of high and low informative value is performed.

In addition, it is explained how a binding volume of services specified for health care (per hospital, per doctor or per combination of hospital and doctor) has affected the quality of the treatment outcome.

If controlled intervention studies are included, the specification of a minimum case volume is considered to be the intervention to be tested. The risk of bias of the controlled intervention studies included is assessed as described in Chapter 9 (see Section 9.1.4).

The results on the target variables reported in the studies are compared and described in the report. Where possible, suitable meta-analytical procedures are used in addition to the comparison of the results of the individual studies (see Section 9.3.7).

5.4 Analysis of data on health care provision

5.4.1 Background

Data on health care provision cover secondary data that describe health care. Secondary data are characterized by the fact that the data are analysed beyond their original, primary purpose. The subsequent use beyond the primary reason for data collection is decisive here [690]. This includes, for example, routine data from SHI funds, data from registries on epidemiological, clinical or intervention-related research questions, or data from population-related health surveys conducted by organizations such as the Robert Koch Institute. In varying detail and depending on the commission, the analysis of data on health care provision comprise the current and systematic description and analysis of health care aspects (often from the perspective of the appropriateness [605], quality and efficiency of services provided within the SHI) of a defined population group regarding a specific medical or system-related research question (see §139a SGB V). In addition to the description of individual aspects of the health care process, individual or complex interventions can be examined. For a planned analysis of data on health care provision, various individual medical, as well as population- and health system-related data, can be used in a modular system, if necessary from different sources.

5.4.2 Aims of an analysis of data on health care provision

The superordinate aim of an analysis of data on health care provision is to describe the provision of health care.

The following aspects can be sub-goals of an analysis of data on health care provision:

- determination of epidemiological indicators
- determination of cost of illness

- determination of health economic indicators (e.g. budget impact analysis, cost-benefit ratios)
- examination of whether the health care provided meets the demand and is appropriate, as well as examination of indications of potential over-, under- or inappropriate provision of health care [605]
- identification of a potential need for research (e.g. clinical research, HTA, health care system research).

For feasibility reasons, the focus within the framework of a project is usually on one or a small number of the aims described above with regard to a certain disease or a certain health care aspect.

5.4.3 Aspects of content of an analysis of data on health care provision

An absolute prerequisite for an analysis of data on health care provision is that the research question to be investigated must be answered with the available data. The formulation of a specific question is therefore necessary for the systematic description and investigation of health care areas. The definition of research questions comprises the specification of the following points:

- population (age; gender; disease; if relevant, subgroup or severity of disease)
- the interventions to be investigated, if applicable (e.g. care of diabetic patients by a general practitioner or a specialist)
- health care setting (e.g. outpatient care, acute inpatient care, long-term care facility, or cross-sector care)
- outcome measures (e.g. number of patients, costs of SHI services)

The analysis of data on health care provision can refer to different levels and/or several health care aspects. Basically, 3 main areas are distinguished: an epidemiological, a health economical, and an area of social organization of health care. The first area covers the distribution and frequency of diseases in the population, on the basis of which the need for medical services can be derived. In this context, specific attention may be paid to certain subgroups of the population (e.g. 'What is the age structure of a disease population with a certain co-morbidity?'). The second area involves the determination of costs or the relationship between costs and benefit of health care interventions. Finally, on a third level, for example, questions concerning the design of health care-related structures and processes of service provision are addressed.

In addition, it may be necessary to take socio-cultural and ethical aspects into account when describing the care of certain patient groups, e.g. consideration of difficult access to health care.

5.4.4 Data sources

Depending on the research question, different data sources can be used to answer it.

Data sources potentially relevant to the respective research question should be defined before the analysis is conducted. Potential data sources are named below (see Table 9).

Table 9: Potential data sources for the analysis of health care

Examples of data	Publicly available	Agreement with data owner required
Health surveys, e.g.: ▪ Health report of federal and state organizations (e.g. German Health Survey for Children and Adolescents by the RKI) ▪ Report of the Federal Statistical Office (e.g. hospital discharge diagnoses, statistics on causes of death).	x	
Registry data, e.g.: ▪ RKI data ▪ Epidemiological and clinical cancer registries	(x)	
Routine data, e.g. from: ▪ Statutory health insurance funds ▪ Associations of Statutory Health Insurance Physicians		x
RKI: Robert Koch Institute		

If potentially suitable data have been identified for a research question, appropriate contractual agreements may be made between the owner of the data and IQWiG, so that the data can be made available for analysis.

As a matter of principle, an assessment of the data structure should precede the analysis, for example with regard to data quality, i.e. completeness and plausibility of the data sets, data collection methods, completeness, and timeliness.

IQWiG addressed the use of data from different sources outside clinical trials for the purpose of benefit assessments of drugs according to §35a SGB V in Rapid Report A19-43 [382].

5.4.5 Methodological features of the analysis of data on health care provision

The complexity of analyses of data on health care provision fundamentally requires an interdisciplinary approach. In addition to clinical expertise, sufficient knowledge of the handling and interpretation of the corresponding data is important.

It is not possible to define a uniform approach for the analysis of data on health care provision. This is strongly dependent on the given framework, such as the main research questions or the data sources used.

Research questions are processed using quantitative methods. When conducting and planning an analysis of data on health care provision, the recommendations of good practice for secondary data analysis should be observed [25].

5.4.6 Presentation of results

A transparent presentation of the methodological approach and results is therefore essential. The method applied must be described in a comprehensible way to ensure replicability. Reporting should be in accordance with the reporting standard for secondary data analysis (STROSA[40]) [689].

[40] Standardisierte Berichtsroutine für Sekundärdatenanalysen

6 HTA reports

6.1 Background and aim

According to §139b (5) SGB V, persons insured in the statutory health insurance (SHI) and other interested individuals can propose assessments of medical examination and treatment methods for selected diseases as well as of questions of quality and efficiency. According to §139b (5) SGB V, this excludes topic proposals where the separate assessment of a drug is the primary focus.

The Institute's task is to select topics from these proposals that are of particular importance to the health care of patients and to process these topics in the form of HTA reports.

The following text describes the process from topic submission to report production.

6.2 Topic collection

Topic proposals for HTA reports can be submitted by persons insured in the SHI and other interested individuals via the website https://www.iqwig.de/en/participation/themencheck-medizin-suggest-a-topic/.

6.3 Selection of topics for the HTA reports

The topics that are proposed up to a yearly deadline run through a multi-step selection procedure (Figure 17). In this context, the perspectives of both the general public and patients as well as the scientific perspective are considered.

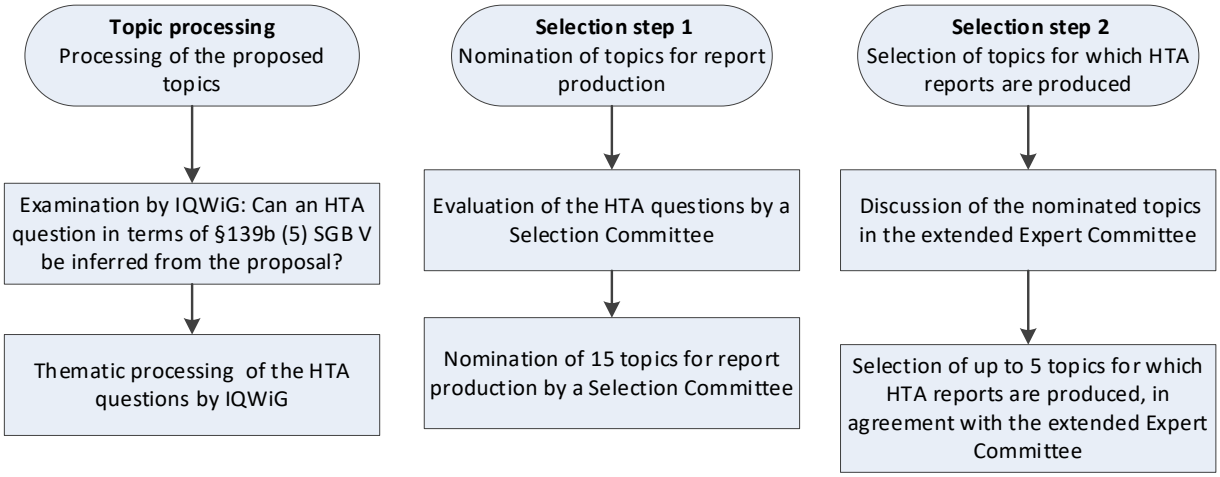


Figure 17: Schematic illustration of the multi-step selection procedure

6.3.1 Selection criteria

For the examination and weighting of topic proposals, as well as after each of the 2 selection steps, the topics proposed are evaluated by means of predefined criteria.

The aim is to select topics that are particularly relevant for the health care of patients. Likewise, as a matter of principle it is specified that medical examination and treatment methods are evaluated. Further criteria and questions that are considered in the selection are, among other things:

- How large is the number of affected persons?
- How great is the disease burden or the severity of disease?
- How comprehensive is the available evidence on the research question?
- Has the research question already been investigated in current HTA reports?
- What costs are related to an intervention?

6.3.2 Evaluation of the research question and processing of topics

The proposals submitted are assessed by the Institute in a timely manner and, if necessary, editorial and qualitative changes are made.

In accordance with §139b (5) SGB V, topic proposals where the focus is on the separate assessment of a drug are excluded from further processing. Therefore only those topic proposals from which an HTA question can be inferred in terms of §139b (5) SGB V are processed further.

For the selection criteria mentioned above (see Section 6.3.1), information on all topics with an HTA question in terms of §139b (5) SGB V is collected and a preliminary search (see Section 8.1.1) is conducted. The results are summarized in the processing of topics.

6.3.3 First step of the selection procedure: nomination of topics

In the first step of the selection procedure, a Selection Committee nominates topics for the production of HTA reports. For this purpose, the processed topic proposals are made available to the Committee. On this basis the Committee selects 15 topics for the production of HTA reports. In this context, the perspectives of both the general public and patients as well as the scientific perspective are considered.

The Selection Committee members comprise firstly, the representatives of organizations recognized on the federal level as relevant for the representation of the interests of patients and self-help groups of chronically ill and disabled persons, secondly, a representative of the Federal Government Commissioner for Patients' Affairs, and thirdly, members of the general public

6.3.4 Second step of the selection procedure: selection of topics for which HTA reports are produced

The topics nominated by the Selection Committee in the first step of the selection procedure are discussed with the extended Expert Committee in the second step. The latter Committee

consists of representatives of organizations forming the Foundation Council of the Foundation for Quality and Efficiency in Health Care as well as a representative of the Federal Ministry of Health. Subsequently, the Institute selects up to 5 topics from the topics nominated by the Selection Committee in consultation with the extended Expert Committee. HTA reports are produced for these topics.

6.3.5 Handling of topics nominated but not selected for HTA production

The topics nominated by the Selection Committee but not selected by the Institute for an HTA report are (once only) again included in the next selection procedure in the following year, where they again pass through the selection steps described in Sections 6.3.3 and 6.3.4.

6.4 Ensuring the quality of HTA reports

The following measures, among others, ensure a high quality of the HTA reports:

- structuring of the content of the HTA reports by the Institute as well as the provision of templates for the HTA report protocol and the preliminary HTA report
- Conformity evaluation of the HTA report protocol, the preliminary HTA report, and the HTA report by the Institute
- production of the HTA report following the Institute's methods
- conduct of systematic searches in the Institute for information in relation to the HTA reports
- conduct of a commenting procedure
- classification of the results of the HTA report in a publisher's comment produced by the Institute

HTA compact is produced by the Institute (cf. Section 2.1.10). It thus undergoes the multistage internal quality assurance procedure provided for all product-specific publications of the Institute (cf. 2.2.4)

6.5 Processing of topics (HTA reports)

As a rule, the HTA reports address all HTA-relevant aspects. Besides the obligatory assessments of the benefit and harm of interventions, following international HTA definition, the economical, ethical, social, legal and organizational aspects of the intervention are also presented in the HTA reports [230,441,479,555].

The level of detail of the investigation of the health economical relevance of the respective examination or treatment method, as well as its ethical, social, legal and organizational aspects, depends on the research question and is specified in the HTA report protocol. The benefit and harm of examination and treatment methods, as well as their economic, ethical, social, legal and organizational aspects, are interlinked. In the processing of these aspects and the

summarized presentation of results, the individual aspects therefore cannot be examined separately from each other.

6.5.1 Benefit assessment

The production of the sections of the HTA report referring to the benefit and harm of examination and treatment methods is conducted using the procedure described in Chapter 3, Section 7.13, and Chapter 9.

6.5.2 Health economics

If a separate health economic analysis is to be prepared in the HTA reports, the requirements of Sections 4.2 to 4.5, 4.7 as well as 4.8 must be considered and the results presented graphically in a coordinate system.

A further option is to generate a systematic review of the available evidence on health economic analyses. In this context, the analyses are in particular assessed with regard to the applicability of the results to Germany, the classification of results under consideration of the methodological requirements described in sections 4.2 to 4.5, as well as the completeness of the data basis.

6.5.3 Ethics

In medicine, but also in public health and health services research, the 4 principles of beneficence, nonmaleficence, respect for patient autonomy, and justice following Beauchamp und Childress [43] are widely disseminated [206,312]. This approach has also been commonly used for the analysis of ethical aspects of medical interventions following HTA methods [42,491]. In recent years further methodological approaches have also been applied. These include, for instance, the Socratic approach, the social shaping of technology, virtue ethics or the triangular approach [26,359]. Depending on the research questions to be processed, the methodological concepts available are suitable in different ways.

The Socratic approach delivers detailed results and has been used for many different medical interventions [198,358,480].The questionnaire by Hofmann 2005 [356,357] is based on the Socratic approach and is as a rule to be used for the HTA reports. If other methodological approaches are better suited, they can also be applied, with corresponding justification in the HTA report protocol.

6.5.4 Social aspects

Social and sociocultural aspects in HTA address the mutual interactions between the examination or treatment method and the social environment (e.g. distribution of resources in a society, access to technologies, patient preferences, societal norms and values). Four approaches for identifying social aspects in HTAs are being discussed: checklists, literature reviews, participatory approaches, and empirical research [276,514]. The framework of Mozygemba et al. [514] is recommended for the examination or exploratory assessment of

sociocultural aspects in HTA reports. A generic questionnaire (e.g. Gerhardus und Stich [276]) or the checklist from the HTA Core Model of EUnetHTA [230] may also possibly be helpful.

6.5.5 Legal aspects

Legal aspects in HTA refer on the one hand to the legal framework in which the examination or treatment method and its assessment are embedded, and on the other hand to the legal aspects related to the implementation and use of the health technology. One distinguishes between technology- and patient-related legal aspects [215,324,753].

6.5.6 Organizational aspects

An HTA report can also examine which interactions arise through an examination or treatment method for the organization of health care and which determinants can influence the implementation of an examination or treatment method. In principle, one can distinguish between the interaction of organizational conditions, procedures and processes and the requirements for health care professionals as well as the decrease or increase in their workload [556]. However, no methodological standard so far exists whereby the organizational interactions of examination or treatment methods in the health care system can be examined [556].

The grid template proposed by Perleth et al. [556] for the assessment of organizational consequences of examination and treatment methods can provide support for the processing of organizational questions.

7 Evidence-based health information for consumers

The Institute has a statutory responsibility to provide readily understandable health information to consumers, but not direct advice to individuals.

In the production of its health information, the Institute adheres to the principles of evidence-based medicine as presented in Section 1.3. This includes applying systematic methods for the scientific assessment of medical interventions as well as integrating the perspective of people affected.

The methods used in the production of evidence-based health information are based on a systematic approach that aims to present the current state of scientific knowledge in an easy-to-understand way, minimize systematic errors (bias) and remain neutral.

To achieve this, evidence-based information is based on the following principles:

- systematic search in the form of targeted information retrieval based on the research questions relevant to the target audience,
- justified selection of evidence appropriate to the research question,
- reasonable and – as far as possible – objective reporting of results that are relevant to patients, such as mortality, symptoms and complications (morbidity) and health-related quality of life,
- appropriate factual and linguistic communication of uncertainties and unclear issues,
- avoidance of any direct recommendations,
- consideration of current evidence concerning risk communication.

These principles apply regardless of the type of commissioning of health information. There are 2 ways of commissioning:

- direct commissions received from the G-BA or the Federal Ministry of Health to produce patient information; these commissions are processed as a report, rapid report or addendum (see Sections 2.1.1, 2.1.2 and 2.1.7),
- the mandate derived from the Institute's statutory responsibility to provide consumers with health information, specified by a general commission from the G-BA (see Sections 1.2 and 7.2)

7.1 Goals of health information

The primary goal of the Institute’s health information is to provide easily understandable medical knowledge that is relevant to decision-making. This knowledge is meant to support the users of information in their autonomy and competency to make an informed decision between different options. This way, users are free to make their own decisions. The information is

written based on the concept of "shared decision-making", according to which users aren't told how to make decisions [213]. Whether to delegate the decision to a doctor or to decide together with others or alone is left up to the individual.

Moreover, the information is to be provided in a way that promotes general health and scientific literacy.

In summary, these are the Institute's goals:

- to provide information that is relevant to medical decisions and easy to understand, even if it concerns complex scientific issues,
- to facilitate active and informed decision-making,
- to promote the critical use of health care services,
- to improve understanding of physical and mental health,
- to improve understanding of medical and scientific information, including the concept of evidence-based medicine,
- to promote the support of patients by family and friends,
- to provide information on handling practical and emotional issues in everyday life,
- to emotionally support people who are affected and
- to help navigate the health care system.

These goals can be summarized as "empowerment". According to the definition of the World Health Organization (WHO), empowerment within a health care system includes the competency to make choices and take actions in accordance with your own goals [533]. Empowering health communication addresses what consumers want to know, shows interest in and respect for patients' opinions, and acknowledges their competence [183,421,734].

The particular challenge of evidence-based health information is in meeting these requirements and goals while being attractive and understandable to users [175]. It is important not to allow the various requirements to result in an overload of information. So it is sometimes not possible to reach all the goals and fulfil all the quality requirements in a single piece of information.

One solution is to combine individual texts and other formats that have different priorities, in order to create information packages of appropriate breadth and depth. This is realized on the websites www.gesundheitsinformation.de (in German) and www.informedhealth.org (in English).

7.2 Selection of topics and identification of information needs

§139a (3) Sentence 6 of SGB V sets the following task for the Institute: "Provision of easily-understandable general information to citizens on the quality and efficiency of health care

services, as well as on the diagnosis of and therapy for diseases of substantial epidemiological relevance".

7.2.1 Topic catalogue in accordance with the statutory responsibility

It is not possible to arrive at a broadly acceptable definition or a clear list of "diseases of substantial epidemiological relevance" based on the literature. One fundamental aspect of epidemiological relevance is a measure of how common a particular illness is. When deciding on which diagnoses or group of diseases to cover, those that affect at least one percent of the public at any given time (prevalence) or within a given year (incidence) are prioritized. This threshold is applied to different subpopulations according to sex and age (0 to 17 years old, 18 to 59 years old, 60 years old and above) in order to reflect the sex- and age-specific particularities of these groups as accurately as possible [433].

The topic catalogue is primarily based on the biannually updated health care report produced by the AOK[41] Research Institute (WIdO[42]) [277]. The report contains information on prevalence and hospitalization rates for the 1500 most common illnesses (grouped according to 3-digit ICD[43]-10 codes), based on about 24 million members of the AOK. The Institute's topic catalogue is reviewed regularly and subsequently amended as needed. This topic catalogue can be expanded, e.g. depending on the topics commissioned to IQWiG or to include medical conditions whose significance and burden of disease cannot be satisfactorily reflected by prevalence or incidence data.

7.2.2 Identification of information needs / Production of information about personal experiences with medical conditions

Ideally, evidence-based health information should be guided by the information needs of the target group. In addition to the general aspects that are relevant to all target groups, such as prevalence and the course of the disease, the information should address topic-specific questions and issues, common misunderstandings and gaps in knowledge.

Patient-centred health information shouldn't just answer medical questions and enable an informed decision. It should also answer questions about health care services and dealing with the disease, as well as offer emotional support [241]. To do this, it is necessary to know the questions users might be interested in. It is also important that the authors at the Institute have an understanding of the situation and the burdens that an illness may cause for patients and their family members. They should develop an understanding of what it means to live with a certain illness.

Therefore, to prepare a topic, qualitative literature is typically searched for and analysed as part of targeted information retrieval (see Section 8.2) in order to identify personal experiences with

[41] Allgemeine Ortskrankenkasse (Local Healthcare Fund, an SHI fund)

[42] Wissenschaftliches Institut der Allgemeinen Ortskrankenkasse

[43] International Statistical Classification of Diseases and Related Health Problems

the condition as well as questions and knowledge gaps that are relevant to the users. The relevant results from Germany are analysed first. If none are available [562], then information needs are derived from studies conducted in similar countries.

Furthermore, freely available health information from other sources on the Internet (e.g. statutory health insurance funds, health authorities, research institutes and commercial businesses) are also reviewed. This provides an impression of the current availability of health information and its main areas of focus. In addition, for different topics, different self-help organisations are contacted and asked about the information needs of patients and the challenges of coping with the illness.

This approach provides a picture of the different stages that a person who is affected by a certain health problem goes through, the associated psychological and emotional problems that can occur, which information is needed, and the points at which decisions need to be made.

7.2.3 Multidimensional patient pathways

Especially for chronic diseases, a sort of map is created to navigate the issues and decisions associated with a given illness. This map shows the possible "pathways" that patients with the disease might take. It should attempt to show as comprehensively as possible how the patient's life may be affected by the illness, and at what points critical decisions are expected.

This approach will be referred to as "multidimensional patient pathways" below.

The decision regarding whether a multidimensional patient pathway will be created for a specific topic will depend on the following criteria, among others:

- Is the illness a long-term or chronic disease that is associated with different stages for the patient (e.g. the processing of a serious diagnosis, unpleasant and difficult treatments, the need for aftercare)?
- Do some of these stages involve complex decisions, such as choosing between various treatment options with specific risk/benefit profiles?
- Are several physicians or other health care professionals involved in the process? Are there different health care options (outpatient or inpatient)?

Multidimensional patient pathways summarize the different social, emotional, cognitive and clinical dimensions that can be associated with an illness. The information is presented in a table. It should illustrate what challenges and decisions patients may face over the course of the illness. The multidimensional patient pathway approach shares similarities with the medical-sociological "illness trajectory" model [145] and the "patient career" model [275,444], as well as various "patient journey" models [451].

One of the aims of multidimensional patient pathways is to determine the scope of a topic and the main areas of focus when producing the Institute's health information. The following questions can be helpful here:

- Who might read the information?
- What questions might the readers have?
- What might be the emotional state of the reader?
- What information might be needed at different points during the course of the disease?
- What decisions are patients faced with, and when and where will they have to make these decisions?
- What effects might health information on this topic have?

This approach mainly aims to help the authors of the Institute's health information systematically develop a good understanding of patients and those close to them, as well as of their interaction with information. Consideration of the dimensions shown in Table 10 supports this aim.

Table 10: Different dimensions of a patient pathway

(Everyday) life	Effects of the disease on social relationships and roles: family and partners, friends, job, quality of life, "performance", etc.
Doing / coping	Any activities related to the illness, such as visiting a doctor, taking medication, looking for information, self-help
Feeling	Feelings that come up during the course of the disease and the treatment, such as grief, fears, worries, etc.
Knowledge	What do consumers already know? What information might they need?
Decisions	What decisions must the person affected make in each phase?
Medical / clinical aspects	Description of the medical phases, such as risk factors, symptoms, diagnosis, treatment, rehabilitation
Contact point in the health care system	Who in the health care or social welfare system can offer help and guidance in each phase, for example, doctors, nurses, physiotherapists, psychotherapists, social workers, information centres, insurance funds?

Various sources are used when producing draught patient pathways. These may include other qualitative literature (qualitative studies and systematic reviews), evidence-based guidelines of national and international scientific associations, evidence syntheses, literature on the information needs of patients and the health care situation, as well as reports of personal experiences with a medical condition [439].

7.3 Information retrieval for the production of health information

When producing evidence-based health information, systematic searches are a key part of the process. They involve scanning current scientific literature for information that is relevant to the research question. As a rule, 2 searches are performed for every topic:

- A search for qualitative literature (see Section 8.2.2): The results are used to identify any needs for additional relevant information, such as personal experiences with the condition. This search is meant to enable the authors to empathize as much as possible with the people affected.
- A search for systematic reviews (see Section 8.2.1): The results provide the basis for drawing conclusions about the benefits and harms of medical interventions.

In addition to these searches, simplified searches (see Section 8.3) are performed to answer specific questions, for instance about the prevalence of the condition.

Searches for systematic reviews aim to identify such overviews of research on all aspects covered in a piece of health information, such as the causes, the course of a medical condition, the prognosis, treatments and epidemiological data. In general, only systematic reviews that are based on searches that were performed in the last 3 years are accepted as a source of information [651,652]. If the searches were performed more than 3 years ago, they may be out-of-date, considering the short half-life of medical knowledge. This time period can be adjusted for specific topics, for example if there is a lack of more recent research.

The identified reviews are then matched with the research questions. In an internal editorial and scientific scoping process, the results of the literature search are used to cover the identified information needs.

If an important information need, such as a need for long-term data, cannot be met with recent systematic overviews, a targeted search for primary studies may be considered.

7.4 Selecting evidence

When producing evidence-based health information, the available relevant scientific knowledge from current and sufficiently reliable studies is to be considered. The type of studies that are appropriate depends on the question being asked. Conclusions about the benefits and harmful effects of interventions are generally based on systematic reviews of randomized controlled trials (RCTs – see Section 8.2). In order to use a systematic review on the effect of an intervention in a piece of health information, the systematic review must meet certain minimum quality standards [397,545,547]. The quality is assessed using the Oxman-Guyatt Index [544,545,547]. Nine items are assessed, including the quality of the information retrieval, the selection of studies and the synthesis of evidence. In order to qualify as a suitable basis for drawing conclusions about the benefits and harmful effects of a medical intervention, a systematic review may have at most minor flaws here. That corresponds to a minimum score

of 5 points. The potential for bias in the included studies must also be assessed regularly at the level of endpoints. In addition, the review authors' handling of possible publication bias must be assessed. For example, was a specific search for unpublished data performed, or were statistical tests used to identify publication bias? Failing to address publication bias or handling it inadequately may lead to a description of the qualitative uncertainty of the results in the health information, or even to the exclusion of the systematic review.

The selection will also be influenced by the question of whether the results are applicable in the context of the German health care system. Aspects taken into consideration include the study population, approval status and how common the intervention is. If conclusions only apply to certain groups, this will be explained in the text.

If a health information article contains conclusions that are based on evidence syntheses of varying qualitative certainty, then this will be addressed in the article.

When more than one systematic review of adequate methodological quality addresses a particular subject or outcome, a further assessment of the systematic reviews is carried out. This way, the qualitatively best reviews can be identified. In addition to the previously mentioned aspects, the following are also considered:

- The main areas of focus of the review, especially with regard to its relevance for patient information
- Sensitivity analyses and handling of heterogeneity

The results of the highest-quality review for a particular research question are taken as the source of the numerical data described in the health information. If reviews come to different conclusions, the possible reasons are explored [398]. These may include differences in the study pool, the statistical analysis or the interpretation of the results.

For research questions on aetiology or prognosis, for instance, systematic reviews on the basis of types of studies other than RCTs can also be used [280]. When assessing such systematic reviews, the criteria of the Oxford Centre for Evidence-Based Medicine are used [341,537]. The methods for assessing qualitative research are described in Section 8.4.

7.5 Choosing the results (endpoints) to be presented

Information on treatment outcomes is based on endpoints that are relevant to patients – in particular mortality, symptoms and complications (morbidity), as well as health-related quality of life. The principles described in Sections 3.1 and 3.2 of these Methods generally apply here.

Further information that is often important to patients includes circumstances surrounding the treatment (e.g. the time involved, physical, mental, social, as well as financial burdens).

7.6 Choosing and presenting comparisons

In order to enable users of gesundheitsinformation.de / informedhealth.org to consider the benefits and harms of an intervention concerning the patient-relevant outcomes described in Section 7.5, a comparison is drawn between having the intervention and forgoing it or using a different standard treatment.

7.7 Handling numerical data and information about risks

Producing a balanced description of the possible benefits and harms of an intervention generally requires a quantification of the effects and risks. This involves taking care to limit the use of numerical data and information about risks so as not to overload the health information, or affect the flow of reading and comprehension.

Because describing probabilities in words often does not lead to a realistic assessment, numbers are preferred [102].

The following principles are followed when providing numbers and probabilities:

- The effect of a medical intervention is described by showing the absolute event frequencies in the comparison groups. Any uncertainties are mentioned. If possible, the reference values will be selected so that the magnitude of the effect is readily apparent.
- The same reference value is used for the descriptions of the benefits and harms, if possible. The starting point for the comparison is the baseline risk, e.g. the natural course of an illness. Here we mean the likelihood that, in the absence of treatment, symptoms will improve, worsen or stay the same. The users will be informed if the symptoms may improve without treatment as well.
- If it is helpful, relative changes will be described in addition to the changes in the absolute risk.

Whether the effects are presented as a "gain" or a "loss" will depend on the particular intervention and the perspective of the person affected by the condition. Here, a uniform frame of reference concerning the benefits and harms is selected. Studies on the benefits of also using diagrams to present numerical information do not clearly show how this affects the endpoints knowledge, risk perception or understandability. The German-language evidence-based guideline *Evidence-based Health Information*[44] arrives at a recommendation that this is optional, based on the low quality of the evidence [477].

In the production of health information, illustrations are mainly used for the supplementary presentation of complex subject matter, e.g. generally in cancer screening decision aids.

[44] Evidenzbasierte Gesundheitsinformation

For the purpose of presenting them in health information, the relative measures of effect that are used in meta-analyses are converted to absolute measures. The absolute effect measure is calculated using a similar approach to that used to produce the results tables within a Cochrane review [351]. The uncertainty of the effect measure is thereby taken into account, but not the uncertainty of the baseline risk [160,669].

The basis of the calculation is a pooled effect estimate from a sufficiently homogeneous meta-analysis. If the effect measure is already a risk difference, it will be used in the further consideration. If a relative effect measure is given, then a plausible baseline risk will first be selected to derive the absolute risk difference. This is typically based on the median of the control group risk in the included individual studies.

In justified cases, the baseline risk can also be derived from a suitable individual study (e.g. the study with the largest by far population or the highest external validity) from the included study pool or from a valid external source (e.g. a German prevalence study, or from registry data). In the event that the baseline risk is taken from an external source and shows a high degree of uncertainty, this uncertainty will be taken into account. The method described by Newcombe and Bender is applied in that case [526].

Based on the assumed baseline risk, the absolute risk in the intervention group and the absolute risk difference are calculated using the relative pooled effect size estimator (odds ratio [OR], relative risk [RR], hazard ratio [HR]) from the meta-analysis.

If the included individual studies have heterogeneous baseline risks, then each absolute effect for the various assumed baseline risks is presented (e.g. for a low and high baseline risk). If it does not make sense to include an absolute effect measure, then it can be left out.

7.8 Taking into account differences related to age and gender

The natural course of a disease, risk factors, symptoms, morbidity, mortality, effects and side effects of interventions, health-related quality of life and accompanying circumstances of an intervention can vary depending on age or gender. If the literature that has been identified as relevant to a condition describes significant differences related to age and gender, these are taken into account while producing health information.

For many topics, the epidemiology of the condition already results in aspects specific to gender and age. If a piece of information is aimed at the group that is mainly affected by a condition, this target audience is not explicitly mentioned in the information.

If no relevant differences between the different groups can be identified, this lack of difference is not specifically pointed out.

If, however, any results apply to subgroups, this is made explicit.

A neutral style of language should ensure that information reaches both women and men and that both genders feel addressed in the same way. Continuously referring to people in the masculine form leads to a mental underrepresentation and linguistic discrimination of women [391]. The information published at gesundheitsinformation.de / informedhealth.org uses a gender-neutral style of language, which avoids the use of generic masculine forms whenever possible. Both genders are explicitly named if both are meant, or gender-neutral expressions are used.

7.9 Adaptation to the target group

A key challenge when producing evidence-based health information is communicating in a way that is understandable while remaining scientifically accurate and objective. Additionally, the Institute's health information is aimed at a heterogeneous target group in terms of literacy, abilities, current health problems, education, personal background, age, and sex. Aspects such as native language and cultural background are also important for some target groups.

When preparing a given topic, a check is done to see whether the epidemiology of the condition results in special requirements for particular target groups.

To meet the needs of specific target groups, the information can be adapted by combining the following options:

- surveys, primary qualitative research and reviews of qualitative research on people's information needs
- experiences of other information providers, patient advice services and self-help groups
- interviews with those affected by the health problem (see Section 9.4.2)
- collection of real-life stories as a separate format (see Section 7.16.2)

7.9.1 Involvement of those affected

There is some evidence that involving the people affected by a particular health problem in the development of health information can increase its relevance [528]. One of the requirements of evidence-based health information [174] is that it takes the consumers' perspective and information needs into consideration. This is a key element when producing health information [772]. This can be achieved in various ways, including the following: When prioritising and narrowing down the aspects to be covered by a topic, ideas proposed by website users and experiences from consultations with self-help groups are taken into account.

Those affected by the medical condition are contacted through the patient representative organisation in the G-BA and through contact with self-help groups.

For suitable topics, the individual stories of patients, as well as those close to them, are presented in order to enable patients and other interested people to find out about the different

aspects of living with a condition and nursing care. This is intended to complement the other health information (see Section 7.16.2).

7.9.2 Non-public commenting procedure

After the internal quality assurance processes and the external expert peer review have been concluded, the Board of Trustees is given the opportunity to comment on the draft version in a non-public commenting procedure. The Board of Trustees also includes representatives of patients' interests and representatives of self-help organizations of chronically ill and disabled people. After the deadline for the submission of comments has passed, the members of the team involved in producing the information and the Head or Deputy Head of the department view the comments submitted and discuss their relevance for the health information. At an editorial conference, the remarks and arguments made in the comments are discussed and – if available – the evidence is reviewed. Any need for revision is agreed upon and documented. The comments are acknowledged close to the time of publication of the final version of the information. If received prior to the deadline, suggestions regarding changes to the content are acknowledged. Comments containing only a few editorial remarks and comments that are received after the deadline are generally not acknowledged. Comments and acknowledgments are not published.

7.9.3 Testing by users

The primary means of testing the understandability of the health information are reviews of drafts by groups of test readers. The standardized external testing by users generally occurs during the same time period as the commenting procedure. It is conducted by an external service provider in the form of focus groups or individual interviews. Depending on the specific topic, patient organizations or other associations or institutions may also participate.

A mix of methods is applied in user testing, including documented individual evaluation and group discussion or individual interviews. Whether a group discussion or individual interviews are conducted is decided depending on the topic of interest. For example, individual interviews may be more suitable for taboo subjects or specific target groups. On the basis of a semi-structured guideline, usually 5 people affected or other potential users test the texts with regard to their content and comprehensibility. The testers are recruited by the external contractor on the basis of criteria specified by IQWiG. The selection criteria relate to the priorities set in the information materials to be tested and usually include information on diagnosis, gender, age, experience with certain treatment options, and, if applicable, social status.

The results of the user testing are considered in the revision of the draft health information.

7.9.4 Users' feedback comments

In addition, users of the website www.gesundheitsinformation.de / www.informedhealth.org can contact the publisher with their feedback. Various channels are offered on the website for this purpose:

- the opportunity to leave comments on individual articles
- a general online contact form
- a randomly generated survey asking individual users to rate the website.

7.9.5 Accessibility

Because the information is primarily offered on the Internet, the website gesundheitsinformation.de / informedhealth.org fulfils the German Barrier-Free Information Technology Regulation (BITV[45]) [105].

The health information is published in both German and English. The availability of an English version improves access for non-German speakers and broadens possibilities for translation into further languages.

7.10 Neutral presentation

Information related to decisions about diagnostic and therapeutic procedures should convey a realistic overview of current knowledge while using non-directive, non-judgmental language and providing an appropriate contextual frame. Any biased and in particular any inappropriately alarming phrasing is to be avoided, as is trivialisation. Both content and language should appropriately reflect significant uncertainties.

In order to convey this requirement to the authors in their daily work, a style guide on text production is used [521]. This guide undergoes continuous development based on the evaluation of our information and emerging evidence in the field of evidence-based communication.

To achieve the goal of neutral presentation, our health information undergoes a multi-stage editorial process including internal quality assurance, an external review, user testing and non-public commenting (see Section 7.9).

7.11 Inferring assessments and recommendations

Individual benefit-risk assessments are based on accurate information concerning patient-relevant outcomes. This aims to enable patients to make decisions in line with their own values and preferences.

Explaining evidence and remaining neutral in communicating health-related information pose a special challenge [217,422,636,710]. As a rule, recommendations are not made in the health information. This is achieved by using non-directive and non-judgmental language. Exceptions are possible, for instance when discussing how to act in the event of an emergency.

[45] Barrierefreie-Informationstechnik-Verordnung

7.12 The development of decision aids

One tool to help people individually weigh benefits and harms are decision aids. The general requirements when producing health information also apply to the content of decision aids. The decision aids are developed according to the International Patient Decision Aid Standards (IPDAS) [214,360].

7.13 Transparency regarding author and publisher

On the websites gesundheitsinformation.de / informedhealth.org and iqwig.de, the Institute outlines its principles and funding as a non-profit and scientifically independent publisher of health information. The information provided exceeds legal requirements and fulfils further transparency criteria.

7.14 Disclosure of relationships

The Institute requires that its staff fully discloses relationships that could influence their work.

Insofar as external reviewers are involved in the production of health information, the same general standards apply as for any other of the Institute's products (see Section 2.2).

7.15 Mentioning of medications, medical procedures and devices

When mentioning medications and medical procedures and devices, generic names are to be preferred. However, as the general public often may not know the names of active ingredients, and instead use colloquial trade names, the Institute's health information may also include trade names.

7.16 Description of typical formats and contents

The website gesundheitsinformation.de / informedhealth.org focuses primarily on the presentation of topics relating to health and illness. One topic may comprise different types of articles and information formats. These different formats are intended to cover the main aspects of a topic and answer central questions users may have. They are also intended to meet the different information needs of different audiences.

The main types of articles include the following:

- **Overview:** The overview introduces the topic and provides background information and links to the types of articles (described below) that further explore the topic. The overview has a fixed structure.
- **Learn more:** This format provides further information on more specific aspects of the topic, such as treatment options with or without medication, or certain diagnostic tests. If possible, a "Learn More" will also describe the advantages and disadvantages of individual treatment options or, if there is not enough good evidence, the resulting uncertainties. A "Learn More" may also offer insights into aspects of living or coping

with a particular health problem. The article will then attempt to take into account both the perspective of the person directly affected by the illness and that of family members or other people who are close to them. “Learn more” articles may be supplemented by illustrations or multimedia content.

- **Research summaries:** These articles are objective summaries of the current knowledge about the question posed in the title. As a rule, they are based on the results of good-quality, systematic evidence syntheses. They provide in-depth descriptions of the studies and explain how the answer to the research question was found.

7.16.1 Supplementary formats

The main formats can be supplemented by additional formats, e.g. to expand on individual aspects of a topic or to try to present certain information in a different way. For example, using images, sound and animated films may increase the attractiveness and understandability of the website, especially for people with lower literacy levels.

The supplementary formats include the following:

- real-life stories of people affected by the medical condition (see Section 7.16.2 for more information),
- illustrations, photos and other images,
- animated films with text and sound,
- quizzes,
- glossary,
- “In brief“: general articles explaining anatomy, bodily functions, treatment approaches and diagnostic measures, as well as the principles and methods of evidence-based medicine,
- calculators.

The goals of these supplementary items include the following:

- promote general understanding of health and medical issues
- help users to understand and weigh up the potential benefits and harms of medical interventions
- facilitate self-management strategies

As a rule, interactive items are also subjected to external testing by users.

7.16.2 Real-life stories

The real-life stories represent one means of conveying scientific evidence and making it accessible to the general public [282]. The importance of real-life stories in medical practice

and in health care is increasingly recognized [293,676,769]. Many patients would like to hear or read about the experiences of people affected by the same health condition as them [344,691].

The essential part of a real-life story is to show how an individual experiences and deals with their situation. Real-life stories provide the following [691]:

- They offer people the opportunity to compare their own experiences with those of others.
- Reading about the feelings of others might "allow" acceptance of similar emotions.
- They can show people who are affected by the medical condition that they are not alone.

By presenting the individual stories of patients as well as those close to them, the Institute makes it possible for patients and other interested people to find out about the different aspects of living with a condition and nursing care. This is intended as a complementary source of health information, in addition to the other products.

Some people may see the real-life stories as a recommendation to make similar decisions. This effect may be in conflict with the aim of creating neutral information. For the real-life stories published on gesundheitsinformation.de / informedhealth.org to first and foremost offer insights into how people experience a medical condition and cope with its effects, the articles are edited to ensure that they

- do not contain any passages that contradict the statements on the scientific evidence contained in the other articles,
- do not make any explicit recommendations, and
- only mention options that are commonly used.

Real-life stories are put together as follows:

- Interview partners are found, most often via self-help organisations, patient universities and doctor's offices.
- Written informed consent is sought regarding the interview procedure and how the interview will be used.
- The interview is conducted (usually by telephone).
- The interviews are documented and edited, and the interview partners give their informed consent for the publication of the final version.
- Publication on the website.

The editing of the interviews includes the transcription of the audio material into German and the reduction of the content to an amount that is suitable for the Internet. The contents are shortened and summarized on the basis of predefined areas of focus, especially in the areas of

living with the condition, experiencing the symptoms, and coping with the diagnosis, course and effects of the disease. This process is carried out in close cooperation with the interview partners.

The methods used to record, edit and publish the real-life stories are guided by the established methods followed by the creators of the Database of Individual Patient Experience (DIPEx) [182].

The decision on whether to include real-life stories in the information on a particular topic is based on various criteria, including the following:

- the possible effects of the illness on patients' lives in terms of physical, emotional and social aspects,
- the possible duration of the medical condition and the likelihood of it becoming chronic,
- the extent to which aspects of the illness are taboo in society, which may make talking about them in a social environment difficult (such as mental illness or conditions affecting the genitals).

7.16.3 Website

The main tool for the dissemination of the health information is the bilingual website www.gesundheitsinformation.de / www.informedhealth.org. High website standards are to be maintained in the following areas:

- usability and accessibility [372,443,527]
- privacy and data protection [384]
- transparency
- search engine visibility [705]
- attractiveness to users

The website includes a free electronic newsletter, with the choice of a fortnightly or monthly subscription. The newsletter contains information on what is new on the website, including when information is updated. The content of the website is also available in Atom and RSS formats, and can be read using the customary readers. In addition, website content can be automatically integrated into other suitable websites through an interface.

The Institute's website is certified by the "Health On the Net" (HON) Foundation, fulfilling the 8 requirements of the HON Code of Conduct (HONcode) for medical and health-related

websites. It also complies with the principles of good practice in the development of health information defined by the German *Good Practice Health Information*[46] [175].

7.17 Updating content

A critical part of providing evidence-based health information is making sure that its conclusions are not out-of-date. Regular updates are one of the quality criteria determined by the EU for health-related websites [141] and described by the German position paper *Good Practice Health Information* [174].

A study of guideline recommendations concluded that after 3 years, over 90% of recommendations may still be up-to-date, compared to only about 50% after 6 years [651]. For some topics, for example where the evidence is very strong, the half-life of evidence may be much longer, and in other areas it may be less than 3 years [652]. The Institute generally considers it necessary to review its information every 3 years. On the basis of this time period, as early as the initial publication of a topic, a deadline is specified for when an update search is to be performed.

Notwithstanding the above, the Cochrane Database of Systematic Reviews (Cochrane Reviews) and the McMaster Online Rating of Evidence (MORE) are checked regularly as part of an orientating evidence scan. German, European, and U.S. regulatory agencies are monitored for health warnings as well.

If a systematic review, study, or announcement found through evidence scanning is identified as being relevant, its effect on the need for an update to health information on related topics is evaluated. The consequences depend on how much the statements in a health information would have to change. This may result in an update ahead of time or go as far as a withdrawal of the health information affected.

7.18 Updating the methods of gesundheitsinformation.de / informedhealth.org

The methods used in the production of health information are reviewed as part of the general update process of the Institute's methods, and revised if there is a need for an update.

[46] Gute Praxis Gesundheitsinformation

8 Information retrieval

Information retrieval for the generation of the Institute's products is conducted in a systematic manner. It can follow quite different goals. The type of goal determines whether comprehensive (see Section 8.1) or focused (see Section 8.2) information retrieval is conducted. In addition, exploratory searches are conducted (see Section 8.3) to search for suitable data on specific research questions in a targeted manner. Starting from a detailed description of the quality standards for comprehensive information retrieval in Section 8.1, only the changes are presented in Sections 8.2 and 8.3. Section 8.4 explains the search for guidelines for the generation of guideline synopses.

In Section 8.5 the approach for assessing information retrieval is described, as conducted within the framework of dossier assessments and assessments of potential as well as assessments according to §137h SGB V.

8.1 Comprehensive information retrieval

Comprehensive information retrieval aims to identify all **relevant** studies and related documents for the respective research question. For this purpose, a systematic search is conducted in several databases as well as in other information sources. The search is usually not limited to specific years. However, a restriction to English and German publications can be made, since evaluations have shown that the exclusion of non-English publications does not change the conclusion of most systematic reviews [327,405,513]. It is checked on a project-specific basis whether a language restriction can be expected to affect the result of the report (e.g. complementary medicine) [507]. Information retrieval is presented in detail in the methods and results section of the report.

Preliminary note: handling reporting bias (including publication bias)

In information retrieval, superordinate aspects such as reporting bias (including publication bias) should be taken into account as they have a fundamental effect on the selection of the different information sources. In this context it should be considered that many research results are never or only partly published [121,501,668] and published studies tend to overestimate the positive effects of interventions and underestimate the negative effects [501,668] (see Sections 3.2.1 and 9.3.13).

In benefit assessments a search for unpublished data is therefore also conducted as a standard component (see Sections 8.1.2 and 8.1.3). Besides unpublished studies, this search should also identify unpublished data from published studies.

Published studies usually appear in scientific journals and thus can largely be searched for via bibliographical databases such as MEDLINE or Embase.

Indications of the existence of unpublished studies and data can, for instance, arise from trial registry entries as well as from clinical study reports prepared by the manufacturers of medical interventions.

If clinical study reports are available, they represent the primary source for the benefit assessment, as only clinical study reports contain nearly all information on a study [434]. In contrast, the information from other sources is often insufficient for a targeted evaluation according to the underlying research question or exhibits discrepancies [411,565,754]. However, data from registry entries and publications can supplement each other [754] or unpublished data can be used to check the correctness of published data [38].

If data are submitted that, according to the will of the persons submitting, are not allowed to be published, these data cannot be considered in assessments, as this would contradict the principle of transparency.

Likewise, the unrequested submission of data, that is, outside the hearing procedures or outside other existing regulations (e.g. queries to manufacturers), are not considered. The unrequested submission of study data bears the risk of selective submission and thus also of subsequent bias in the result of the benefit assessment.

8.1.1 Searches in bibliographic databases

Bibliographical databases (besides trial registries) represent a main source for identifying study results, especially if no clinical study reports are available. The detailed procedure is described below.

A) Preparatory searches

At the start of a project, before the development of the actual search strategy, preparatory searches are usually conducted (e.g. by means of an exploratory search). The searches serve to prepare the project. For this purpose, a search is conducted in particular for existing systematic reviews [129,255,674], but also for potentially relevant primary studies on the topic.

For the conduct of these searches, sources such as the Cochrane Library as well as websites of HTA agencies such as the UK National Institute for Health and Care Excellence (NICE) or the US Agency for Healthcare Research and Quality (AHRQ) can be searched to identify systematic reviews [231,674,752]. In addition, if appropriate, earlier IQWiG reports, published manufacturer dossiers as well as resolutions by the G-BA can be screened. To identify **ongoing** HTA reports and systematic reviews, further databases such as the Prospective Register of Systematic Reviews (PROSPERO) [128] can be considered. Furthermore, guidelines or clinical information systems such as Dynamed or UpToDate can be used as an information source.

If no relevant systematic reviews are found, an iterative process is conducted using different search techniques (see Section 8.1.4) such as citation-based techniques [144,333] or the use of the “similar articles” function in PubMed (see Section 8.1.4) [333]. The starting point is formed

by several relevant articles that are already known or were found by a very precise search. In several runs articles are then identified and tested for relevance [574,625].

B) Structure of a search strategy

Before the development of a search strategy the structure of the search must be specified. For this purpose, a clearly formulated research question is required. Formulation based on PICOS[47] is mostly a useful approach to structure the search [457]. In this context only the most important search components are used to develop the search strategy [626]. The search strategy mostly contains search terms on the therapeutic indication, intervention and study type [457].

C) Selection of databases

A systematic search in several bibliographic databases is required for the production of systematic reviews [592,593,611,685].

Recent analyses show that most published studies can be found in a limited number of databases [5,288,313,326]. The Cochrane Handbook lists MEDLINE, Embase and CENTRAL[48] as the 3 most important bibliographic databases (for primary studies [457]). These are also the most frequently used databases for systematic reviews [66].

Depending on the research question of the benefit assessment, regional or topic-specific databases can also be considered.

D) Development of search strategies

A combination of subject headings (including publication type) and free-text terms is necessary for the development of search strategies [267,404,418]. An objective approach for developing search strategies is characterized by the fact that text analysis procedures are used for identifying free-text terms and subject headings [554,673]. For instance, IQWiG's objective approach is based on the analysis of relevant articles already known [331,334]. In this context different text-analysis tools such as Wordstat [567] and AntConc [23] are used. In a next step the search terms selected are allocated to the single concepts of the search strategy [615,626].

If available, validated study filters (e.g. for RCTs [205,457,764,765] and systematic reviews [764] or validated classifiers from machine learning (e.g. RCT classifiers [490,740]) are used. For other study types or questions, it should be checked in the individual case whether validated study filters are available that can be applied reliably. For example, there is a controversial discussion about the use of search filters in the search for diagnostic accuracy studies [57]. Study filters cannot always be used when searching for non-randomized studies [332], even though validated filters for specific study types are now available [739].

[47] Population, intervention, comparison, outcome, and study design

[48] Cochrane Central Register of Controlled Trials

Furthermore, an additional search for non-indexed data sets in PubMed/MEDLINE can be conducted. This especially aims to identify very recent citations [201,702]. This search is based on free-text terms with an adaption of study filters [154,402], as these filters are usually optimized for a combination of subject-heading and free-text searches.

E) Quality assurance of search strategies

A high-quality search strategy is a prerequisite for ensuring the completeness of the evidence base of a benefit assessment [614,615]. Due to their complexity, search strategies for bibliographic databases are error prone [612]. The PRESS[49] checklist is therefore used to support the process of quality assurance [498].

Quality assurance with the PRESS checklist is initially a formal evaluation and is always performed before the conduct of searches. In addition to the PRESS checklist, the search strategy is tested against an independent set of relevant citations [613]. It is thus evaluated in advance whether the set of relevant citations can be found by the search strategy.

F) Study selection

Due to the primarily sensitive approach, the literature search in bibliographic databases results in a large number of citations that are not relevant to the assessment. The selection of relevant publications is made in several steps:

- Exclusion of definitely irrelevant publications (i.e. publications not fulfilling the inclusion or exclusion criteria of the report plan or project outline) through perusal of the titles, and, if available, the abstracts [490].
- The full texts of the remaining potentially relevant publications are obtained. The decision on the inclusion of the study in the assessment concerned is then made on the basis of these documents.

All selection steps are performed by 2 persons independently of each other. Discrepancies are resolved by discussion. In the first selection step, if doubts exist as to the relevance of a study, the corresponding full text is obtained and assessed.

The documentation of study selection is performed as transparently as possible and contains the decisions on the inclusion or exclusion of each citation (only on the full-text level) [129,209]. Study selection is performed in IQWiG's internal web-based trial selection database (webTSDB [330]). The references evaluated are further documented in the course of report production using the reference management software Endnote [136].

[49] Peer Review of Electronic Search Strategies

G) Documentation in the report

A clear and transparent presentation of all aspects of the search enables the assessment of the quality and completeness of the systematic search [550,575,616] as well as the conduct of later search updates.

As a standard, for the search in bibliographic databases, the following items adapted from the PRISMA-S[50] guideline [575] are documented:

- databases used, as well as database providers and search interfaces
- the search period and the last search date
- the search strategies with all search limitations

In addition, the selection process is presented in the results section of the report by means of a flowchart [129,209,549,550,574] and the citations of the studies or documents included or excluded are presented in separate reference lists [647].

8.1.2 Searches in trial registries

The importance of trial registries has strongly increased in the past years. For instance, since 2005, the International Committee of Medical Journal Editors has required the prospective registration of clinical studies as a precondition for publication in scientific journals [158].

In addition, since 2007 there has been a legal obligation in the United States to register nearly all clinical studies regulated by the FDA as well as their results [2]. If available, ClinicalTrials.gov now provides links to the study protocol, the statistical analysis plan (SAP) and the data sharing statement of a study [524,693,768].

Since 2011, the European Medicines Agency (EMA) has also been publishing data on the registration of a large part of its approval studies for drugs via the EU Clinical Trials Register (EU-CTR) [229] and has also been publishing study synopses in this registry since July 2014 [229].

A) Structure of a search strategy

Searches in trial registries should show high sensitivity, be simple, and, if possible, only consider one component (usually the therapeutic indication or intervention) [278]. Firstly, terms for the concept that can best be depicted (generating the least number of hits, despite high sensitivity) are included in the search. The search is only further restricted with the second concept if too many hits are retrieved. Due to the differing quality of the individual entries, a further restriction (e.g. according to study status) is only to be undertaken in exceptional cases.

[50] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (-for Searching)

B) Selection of trial registries

A systematic search always considers several trial registries, as no trial registry includes all studies [133,278,692]. The search is at least conducted in ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) Search Portal of the WHO [38,278,457]. The ICTRP is a meta-registry that includes a large part of clinical studies [133,319]. However, the search functions are very limited [278,429] and the trial registry regularly produces error messages [329]. Important trial registries such as ClinicalTrials.gov are therefore searched directly, even though they are also covered via the ICTRP [278,429].

In addition, the EMA registry EU-CTR should be considered for benefit assessments of drugs. Furthermore, trial registries of the pharmaceutical industry (registries of individual companies) and the Drug Information System (AMIce[51]) of the Federal Institute for Drugs and Medical Devices (BfArM[52]) [104] can also be searched. This database includes results reports of studies conducted outside Europe and the United States.

C) Further procedure

The procedure for trial registries regarding quality assurance, conduct of the search, study selection, documentation, as well as search updates largely follows the search in bibliographic databases. There is one exception: the trial registry entries are selected in a one-step procedure, as the complete information is directly available via the website of the trial registry.

8.1.3 Requests to manufacturers

For the benefit assessment of drugs or procedures largely based on a medical device, the manufacturers of the technologies to be assessed are usually asked to provide previously unpublished information. The aim of this request is to identify all relevant information on these studies, independent of their publication status.

The basis for the incorporation of previously unpublished information into the benefit assessment is the conclusion of an agreement on the transfer and publication of study information. This agreement is made between the Institute and the manufacturer involved before the submission of data (see sample contract for drugs [legally-binding German version and English translation] [374]). It specifies the procedure, the requirements for the documents to be submitted, and their confidential and non-confidential components.

This request is usually made in 2 steps. In the first step, the Institute asks the manufacturer to supply a complete overview of all studies conducted by the manufacturer. In this context, the Institute defines the project-specific inclusion criteria for this overview. In the second step, the Institute identifies studies relevant to the benefit assessment from the overview, and requests detailed information on these studies. This may refer to a request for unpublished studies, or for supplementary, previously unpublished information on published studies. Previously

[51] Arzneimittel-Informationssystem

[52] Bundesinstitut für Arzneimittel und Medizinprodukte

unpublished information considered in the benefit assessment is also published in the Institute's reports in order to ensure transparency.

If the manufacturer concerned does not agree to this contract and therefore does not agree in particular to the complete transfer of all information requested by the Institute, or does not completely transfer the information requested despite conclusion of the agreement, no further requests to the manufacturer will be made. This is to prevent biased results due to the selective provision of information (see Section 3.2.1).

8.1.4 Further information sources and search techniques

To identify further relevant studies or documents, depending on the research question, further information sources are used and further search techniques applied.

With regard to study selection and documentation in the report, differences arise that result partly from the limited search options and partly from the type of data searched. For instance, certain information sources are only screened by one person with regard to studies, who then assesses these studies in respect of their relevance; a second person checks the whole process including the assessments (e.g. publicly accessible documents of regulatory authorities, screening of reference lists).

The following text presents further information sources and search techniques that are considered either as a standard or optionally in the benefit assessment.

A) Regulatory authorities

If drug assessments or treatment methods largely based on a medical device are assessed, publicly accessible documents from regulatory authorities are a potential source for information retrieval.

Documents of regulatory authorities

Information on drugs approved centrally in Europe (e.g. European Public Assessment Reports, EPARs) is searched for via the EMA website [222]. In the United States, access to the FDA's Medical Reviews and Statistical Reviews is provided via Drugs@FDA [717].

In contrast to the United States, there is no central approval procedure for medical devices in Europe. Publicly available information on medical devices is currently only occasionally available in individual countries, for example at NICE via the "List of interventional procedures" [522]. In future, the results of studies on new implantable and class III devices are to be made (partly) publicly accessible in the European Database on Medical Devices (EUDAMED) [221]. In the United States, information on medical devices evaluated by the FDA, including the information on the underlying data basis, can be searched for via Devices@FDA [716].

B) Selected scientific journals and conference proceedings

Depending on the research question, it can be useful to conduct a handsearch in selected scientific journals. This is decided on a case-by-case basis. A search of conference proceedings is usually dispensed with, as these documents usually contain little information on study methods and results [202].

C) Documents transferred by the G-BA or Federal Ministry of Health

If documents are provided by the contracting agency (G-BA or Federal Ministry of Health), they are evaluated with regard to whether they refer to studies that fulfil the inclusion criteria of the assessment.

D) G-BA website and IQWiG website

Depending on the research question, it can be useful to screen the G-BA and IQWiG websites for previous IQWiG products, publicly accessible manufacturer documents (e.g. Modules 1 to 4 of dossiers on early benefit assessments pursuant to §35a SGB V), as well as G-BA resolutions with regard to whether studies are mentioned that fulfil the inclusion criteria of the assessment.

E) Application of further search techniques

Different search techniques have been established for preparatory searches at the start of projects, for research questions that are difficult to search for (e.g. complex interventions), and for the evaluation of search strategies in bibliographic databases [333]. These include citation-based search techniques (such as the screening of reference lists and citation tracking) as well as the use of the "similar articles" function. For all benefit assessments, the screening of reference lists of systematic reviews is usually conducted as an additional search technique.

F) Hearing

Studies or study information transferred within the framework of the hearing on the preliminary report plan or on the preliminary report are considered.

G) Requests to authors

If the available information on a study is incomplete, unclear, or contradictory, it may be useful to contact the authors of study publications. These requests can be undertaken to better evaluate the suitability, the methodological quality or results of a study [209,516,574]. Such requests are usually undertaken only if a relevant impact on the report can be expected.

8.2 Focused information retrieval

It is not necessary or possible to conduct information retrieval targeted towards completeness for all research questions. In such cases, so-called focused information retrieval is conducted, especially if the requirement of a systematic and transparent approach still exists.

Focused information retrieval is, for example, conducted 1) for projects with a short processing time (e.g. dossier assessments, evidence reports), 2) if a research question is not targeted towards completeness (e.g. in qualitative research), or 3) if the assessment is to be based on systematic reviews. Focused information retrieval aims to achieve a balanced relation between sensitivity (i.e. completeness) and precision (i.e. accuracy).

The approach regarding the development of the search strategy, quality assurance, conduct of the search, study selection and documentation is based on comprehensive information retrieval (see Section 8.1). However, restrictions or adaptions can be undertaken in the following areas, for example, as frequently applied in the area of rapid reviews [577,578,711]:

- in the selection of databases
- in the selection of study filters
- in the restriction of search periods (publication years) and/or languages
- in the selection of studies (performed by one person; quality assurance of the results by a second person)
- in the presentation of methods and results

In addition, fewer information sources are often considered.

8.2.1 Search for systematic reviews

In the search for systematic reviews it is sufficient if a large proportion of the high-quality and current systematic reviews on a research question is identified. In this context the search is conducted in at least the following databases:

- MEDLINE
- the HTA Database, and
- the Cochrane Database of Systematic Reviews

Precise study filters are applied in the development of search strategies (e.g. the "High specificity strategy" [763]). If necessary, the search period of the search is restricted. For example, as a rule searches for systematic reviews used as a basis for health information are restricted to the last 3 years.

In addition, systematic reviews can be used as a source for primary studies in order to conduct a benefit assessment based on these studies [582]. For this purpose, an assessment of the inclusion and exclusion criteria, as well as the information retrieval in the systematic review(s) identified, is conducted beforehand (based on e.g. Item 3 of the AMSTAR[53] checklist [647]). One (or potentially several) high-quality and current systematic review(s) is/are then chosen,

[53] Assessment of Multiple Systematic Reviews

and the primary studies considered are extracted and then selected. In this approach only the search results of the systematic review used are taken over, but not the assessment of the primary studies included or the data extraction. In addition, an update of the information retrieval according to Section 8.1 is conducted for the period not covered by the systematic review(s) (see Section 8.2.1).

If information sources listed in the report plan or project outline were not considered in the systematic review or not searched comprehensively (e.g. trial registry), these sources can be searched within the framework of information retrieval for the benefit assessment.

8.2.2 Search for qualitative research

In the search for literature on qualitative research, among other things, experiences related to a certain disease are to be recorded, problems in copying with the disease and its treatment identified, as well as potential needs for information inferred.

A search is conducted at least in MEDLINE and CINAHL[54] and, if necessary, supplementary in topic-specific bibliographic databases such as PsycINFO[55].

8.2.3 Search for health economic questions

There are very different health economic questions for which focused information retrieval is to be conducted. These include the search for health economic evaluations, decision analytic models, the measure of overall benefit, cost determination, as well as, if necessary, epidemiologic data, if no data from Germany are available.

A search is conducted in at least the bibliographic database MEDLINE. In addition, manufacturers can be asked to provide health economic evaluations.

8.2.4 Searches within the framework of addenda to §137e or §137h assessments

Focused information retrieval is conducted within the framework of addenda to §137e or §137h assessments.

A systematic search is conducted in bibliographic databases:

- MEDLINE
- Embase, and
- CENTRAL

In addition, a search is conducted in the trial registries ClinicalTrials.gov and the ICTRP Search Portal.

[54] Cumulative Index to Nursing and Allied Health Literature

[55] American Psychological Association's database of psychology abstracts

8.2.5 Checking the completeness of a study pool

An assessment of the information retrieval in dossiers is performed within the framework of dossier assessments (see Section 8.5). Depending on the result, a check of completeness is performed, which aims to check the completeness of the study pool presented; it does not aim to identify the complete data basis.

A search in the following trial registries is conducted

- ClinicalTrials.gov
- ICTRP Search Portal, and
- EU-CTR

As a supplementary search, in certain cases (e.g. search for studies of drugs approved before 2007; search for study types other than RCTs [380]) a bibliographic search is additionally conducted using the combination of different search techniques (simple Boolean search as well as the "similar articles" function in PubMed [617,738]).

8.3 Exploratory searches

An exploratory search is a targeted search for suitable data. The search ends as soon as the information required is available.

The information sources are very topic dependent and often comprise clinical information systems such as Dynamed and UpToDate or guideline databases. In addition, depending on the research question, specific data collections are used, such as those of the Robert Koch Institute, the Federal Statistical Office or the AOK[56] Research Institute (WIdo[57]), as well as data from regional registries, laws, regulations or directives.

In contrast to comprehensive information retrieval, the search for and selection of data is performed by one person. Quality assurance of the result is performed by a second person. Documentation in the report is restricted to the presentation of specific results.

Examples of exploratory searches are preparatory searches at the start of projects (see Section 8.1.1) as well as searches for cost data (see Section 4.4.4) and for epidemiological data (see Section 4.5.2).

[56] Allgemeine Ortskrankenkasse (Local Healthcare Fund, an SHI fund)

[57] Wissenschaftliches Institut der Allgemeinen Ortskrankenkasse

8.4 Search for guidelines for the production of guideline synopses

If the aim of the search is to identify clinical practice guidelines, it is conducted in guideline databases (e.g. the AWMF, the Canadian Medical Association [CMA] Infobase, and the Trip Database) and on the websites of providers of specialist and multi-disciplinary guidelines.

For the search in guideline databases or websites of guideline providers, the search strategy to be applied is targeted towards the structure and options of the particular websites. Only a few websites allow a search with key words, so that generally the complete list of a website's published guidelines is screened. In addition, for the search in guideline databases or websites of guideline providers, a standardized export is often not possible. For this reason, the search and number of hits are documented in a standardized search protocol. The potentially relevant hits are documented in a reference management programme. The procedure of the selection of guidelines is conducted as presented in Section 5.2.2. However, within the framework of the search in guideline databases and websites of guideline providers, depending on the research question, in a supplementary step it is evaluated whether a methodological system was used in the development of the guideline. This usually means whether a guideline is evidence based or not (see Chapter 5). Within the framework of the production of the report plan, the inclusion and exclusion criteria are specified a priori.

Title and abstract screening is performed by one person; the quality assurance of this step is performed by a second person. The following steps (from the full-text screening) are performed by 2 persons independently of each other.

Within the framework of guideline appraisal it can be useful in the individual case to contact authors of publications on guidelines or guideline developers. The requests can refer, for example, to specific details of individual guidelines or to non-published partial aspects of publications.

8.5 Assessment of information retrieval

In the preparation of a dossier or application for testing, a search in bibliographic databases and a search in publicly accessible trial registries must as a matter of principle be conducted by the applicant; the precise requirements are provided in the G-BA's Code of Procedure [268,271]. In a similar way, hospitals preparing information on an assessment in accordance with §137h SGB V must systematically search for information on the method requested.

The Institute conducts an evaluation of the information retrieval documented in the presented documents for dossier assessments, assessments of potential, and assessments in accordance with §137h SGB V. For all 3 assessment procedures, the searches in bibliographic databases and trial registries, as well as the study selection, are evaluated. This evaluation is based on the procedure described in Section 8.1.1 regarding the quality assurance of search strategies, as well as on the document templates included in the requirements of the G-BA's Code of Procedure [268,271].

Noticeable issues in the assessment of dossiers

Depending on the results arising from the assessment of the dossiers, different strategies are available to check the completeness of information retrieval. For example, random checks of the literature citations excluded in the dossier can be performed or the Institute can conduct its own search and/or study selection by means of a check of completeness (see Section 8.2.5). If a high number of hits is retrieved, the comparison can also be performed on the basis of systematic reviews (see Section 8.3 or 8.2.1). The result of the check of the completeness of information retrieval and the description of the approach in this regard form part of the dossier assessment.

9 Assessment of information

As a matter of principle, the step of information retrieval (see Section 7.13) is followed by an assessment step in which the information retrieved is systematically assessed with regard to its informative value. This chapter primarily explains the aspects that apply to the assessment of information within the framework of benefit assessments.

In research the term "bias" means a systematic deviation between research results and the "truth" [606]. For example, this may refer to an erroneously too high (or too low) estimation of a treatment effect. A main objective in the benefit assessment of medical services is to estimate the actual effect of therapies and interventions as reliably and unbiasedly as possible. In order to minimize bias in the benefit assessment of medical services, different approaches are adopted internationally; these include using scientifically robust methods, ensuring wide participation in the relevant studies, as well as disclosure of relationships. All these methods also form the legal basis of the Institute's work.

9.1 Quality assessment of individual studies

9.1.1 Criteria for study inclusion

The problem often arises that studies relevant to a benefit assessment do not completely fulfil the inclusion criteria for the patient population and/or the test and comparator intervention defined in the systematic review. In this case the Institute usually proceeds according to the following criteria:

For the inclusion criterion with regard to the study population, it suffices if at least 80% of the patients included in the study fulfil this criterion. Analyses of the relevant subpopulation are drawn upon if they are available in such studies. Studies in which the inclusion criterion for the study population is fulfilled in less than 80% of the patients included in the study are only included in the analysis if analyses of the relevant subpopulation are available, or if it has been demonstrated with sufficient plausibility or has been proven that the findings obtained from this study are applicable to the target population of the systematic review (see also Section 3.3.1 for applicability).

Studies are also included in which at least 80% of patients fulfil the inclusion criterion regarding the test intervention (intervention group of the study) and at least 80% fulfil the inclusion criterion regarding the comparator intervention (comparator group of the study). If 1 of the 2 criteria is violated in a study, it is excluded from the benefit assessment.

It is essential that at least the most relevant information on a study is available to allow use of the study results. Submissions to scientific meetings, published abstracts or press releases on studies usually contain far too little and unreliable information on study methods and results to allow use of these sources for benefit assessments [361].

In order to assess the usability of a source, the Institute follows the various statements that have been prepared to improve the quality of publications. These include, among others:

- the CONSORT[58] statement on RCTs [632] and the corresponding explanatory document [506]
- a proposal for an extension of the CONSORT statement for randomized studies on non-drug interventions [74] and the corresponding explanatory document [73]
- the CONSORT statement on cluster-randomized trials [119]
- the CONSORT statement on the documentation of adverse events [388]
- the CONSORT statement on non-inferiority and equivalence studies [561]
- the CONSORT statement on pragmatic studies [773]
- the CONSORT PRO extension for PROs [118]
- the CONSORT extension for multi-arm randomized trials [415]
- the TREND[59] statement on non-randomized intervention trials [165]
- the STROBE[60] statement for observational studies in epidemiology [737] and the corresponding explanatory document [726]
- the TRIPOD[61] statement for prognostic studies [140] and the corresponding explanatory document [512],
- the STARD[62] statement on diagnostic studies [70,71] and the corresponding explanatory document [72]
- die ISOQOL[63] reporting standards for PROs [100]

9.1.2 Relation between study type and research question

Only the most relevant study designs that play a role in benefit assessments in medical research (depending on the research question posed) are summarized here.

It is primarily the inclusion of a control group that is called for in the benefit assessment of interventions. In a design with dependent samples without a control group, proof of the effect of an intervention cannot usually be inferred from a pure "before-after" comparison. Exceptions include diseases with a deterministic (or practically deterministic) course (e.g. ketoacidotic diabetic coma or ventricular fibrillation; see Section 3.2.2). Randomization and blinding are

[58] Consolidated Standards of Reporting Trials

[59] Transparent Reporting of Evaluations with Non-randomized Designs

[60] Strengthening the Reporting of Observational Studies in Epidemiology

[61] Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

[62] Standards for Reporting of Diagnostic Accuracy

[63] International Society of Quality of Life Research

quality criteria that increase the informative value of controlled studies. Parallel group studies [564], cross-over studies [410], and cluster randomized studies [195] are common designs for clinical trials. If interim analyses are planned, the use of appropriate sequential designs must be considered [410].

Case reports or case series often provide initial information on a topic. These are susceptible to all kinds of bias, so that, depending on the research question, only limited reliable evidence can be inferred from this type of study. The prevalence of diseases can be estimated from population-based cross-sectional studies. Other fundamental and classical study types in epidemiology are case-control studies [78] to investigate the association between exposures and the occurrence of rare diseases, as well as cohort studies [79] to investigate the effect of an exposure over time. Cohort studies designed for this purpose are prospective, although retrospective cohort studies are also conducted in which past exposure is recorded (this type of study is frequently found in occupational or pharmacological epidemiology). In principle, prospective designs are preferable to retrospective designs. However, case-control studies, for example, are frequently the only feasible way of obtaining information on associations between exposures and rare diseases. Newer study designs in modern epidemiology contain elements of both case-control and cohort studies and can no longer be clearly classified as retrospective or prospective [417].

Diagnostic and screening studies may have very different aims, so that the assessment depends on the choice of an appropriate design (see Sections 3.5 and 3.6).

9.1.3 Ranking of different study types / evidence levels

Different approaches exist within the framework of systematic reviews or guideline development for allocating specific evidence levels to particular study types [310,317]. These levels can be used to create a ranking with regard to the validity of evidence from different study types. However, no system of evidence assessment currently exists that is generally accepted and universally applicable to all systematic reviews [419,745]. Due to the complexity of the appraisal of studies, no conclusive judgement on quality can be inferred from the hierarchy of evidence [29,761]. According to EBM standards, the Institute follows the rough hierarchy of study types, which is widely accepted and is also largely consistent with the evidence classification of the Fourth Chapter §7 (3) of the G-BA's Code of Procedure [271] and has been incorporated in the regulation on the benefit assessment of drugs according to §35a SGB V [106]. At least for the evaluation of intervention effects, the highest evidence level is allocated to RCTs and systematic reviews of RCTs. In some classifications, individual RCTs are further graded into those of higher or lower quality (see Section 3.1.4).

However, at the latest in the classification of non-randomized studies with regard to their risk of bias, the study design alone can no longer provide sufficient orientation [308,346,735], even if the basis distinction between comparative and non-comparative studies seems meaningful. As described in Section 3.8, in the classification of non-randomized studies, besides other design aspects the Institute will primarily evaluate the control for potential confounders.

However, this grading refers to the risk of bias (see Section 9.1.4) and not to the evidence level of the study.

9.1.4 Aspects of the assessment of the risk of bias

One main aspect of the interpretation of study results is the assessment of the risk of bias (see qualitative uncertainty of results, Section 3.1.4). In this context, the research question, the study type and design, and the conduct of the study play a role, as well as the availability of information. The risk of bias is substantially affected by the study quality; however, its assessment is not equivalent to the quality assessment of a study. For example, individual outcomes may also be considerably biased in a high-quality study. Other studies, however, may provide high certainty of results for specific outcomes in individual cases, despite being of low quality. As a rule, the Institute will therefore estimate the extent of the risk of bias in a problem-orientated manner for all relevant results (both for the study and the specific outcomes).

In principle, a recognized standardized concept should be followed in a study; from planning to conduct, data analysis, and reporting. This includes a study protocol describing all the important methods and procedures. For (randomized) clinical trials, the usual standards are defined by the basic principles of good clinical practice (GCP) [385,435]; for epidemiological studies, they are defined by guidelines and recommendations to ensure good epidemiological practice (GEP) [168]. In this context, a key criterion to avoid bias is whether the study was actually analysed in the way planned. This cannot usually be reliably concluded from the relevant publications. However, a section on sample size planning may at least provide indications in this regard. In addition, a comparison with the study protocol (possibly previously published) or with the corresponding publication on the study design is useful.

Key aspects of the Institute's risk-of-bias assessment of the results of RCTs comprise

- adequate concealment, i.e. the unforeseeability and concealment of allocation to groups (e.g. by external randomization in trials that cannot be blinded)
- blinded outcome assessment in trials where blinding of physicians and patients is not possible
- appropriate application of the "intention-to-treat" (ITT) principle [679].

There must be a more cautious interpretation of the results of unblinded trials, or of trials where unblinding (possibly) occurred, compared with the interpretation of blinded studies. Randomization and the choice of appropriate outcome variables are important instruments to prevent bias in studies where a blinding of the intervention was not possible. In studies that cannot be blinded, it is crucial to ensure adequate concealment of the allocation of patients to the groups to be compared. It is also necessary that the outcome variable is independent of the (non-blinded) treating staff or assessed in a blinded manner independent of the treating staff (blinded assessment of outcomes). If a blinded assessment of outcome measures is not possible, a preferably objective outcome should be chosen which can be influenced as little as possible

(with regard to its dimension and the stringency of its recording) by the (non-blinded) person assessing it.

Standardized assessment forms are used to assess the risk of bias. As a rule, for controlled studies on the benefit assessment of interventions the following items across and specific to outcomes are considered in particular:

Items across outcomes:

- appropriate generation of a randomization sequence (in randomized studies)
- allocation concealment (in randomized studies)
- temporal parallelism of the intervention groups (in non-randomized studies)
- comparability of intervention groups and appropriate consideration of prognostically relevant factors (in non-randomized studies)
- blinding of patients and treating staff/staff responsible for follow-up treatment
- reporting of all relevant outcomes independent of results

Outcome-specific items:

- blinding of outcome assessors
- appropriate implementation of the ITT principle
- reporting of individual outcomes independent of results

On the basis of these aspects, in randomized studies the risk of bias is summarized and classified as “high” or “low”. A low risk of bias is present if it can be excluded with great probability that the results are relevantly biased.

In the assessment of an outcome, the risk of bias across outcomes is initially classified as “high” or “low”. If classified as “high”, the risk of bias for the outcome is also classified as “high”. Apart from that, the outcome-specific items are taken into account.

The classification as “high” of the risk of bias of the result for an outcome does not lead to exclusion from the benefit assessment. This classification rather serves the discussion of heterogeneous study results and affects the certainty of the conclusion.

No summarizing risk-of-bias assessment is usually performed for non-randomized comparative studies, as their results generally carry a high risk of bias due to the lack of randomization. When assessing individual aspects of the risk of bias, the Institute follows the criteria of the

ROBINS-I[64] instrument [678]. The Institute specifically deviates from this procedure in assessments of the potential of new examination and treatment methods (see Section 3.8).

The QUADAS-2[65] criteria [750,751] are considered for the assessment of diagnostic accuracy studies; these criteria are adapted to the specific project, if necessary. The PROBAST[66] instrument [762] is primarily used for the methodological assessment of prognosis studies (see Section 3.5).

If a project of the Institute involves the assessment of older studies that do not satisfy current quality standards because they were planned and conducted at a time when these standards did not exist, then the Institute will present the disadvantages and deficiencies of these studies and discuss possible consequences. A different handling of these older studies compared with the handling of newer studies that have similar quality deficits is however only necessary if this is clearly justifiable from the research question posed or other circumstances of the assessment.

The assessment of formal criteria provides essential information on the risk of bias of the results of studies. However, the Institute always conducts a risk-of-bias assessment that goes beyond purely formal aspects in order, for example, to present errors and inconsistencies in publications, and to assess their relevance in the interpretation of results.

9.1.5 Interpretation of composite outcomes

A so-called composite outcome comprises a group of events defined by the investigators (e.g. myocardial infarctions, strokes, cardiovascular deaths). In this context the individual events in this group often differ in their severity and relevance for patients and physicians (e.g. hospital admissions and cardiovascular deaths). Therefore, when interpreting composite outcomes one needs to be aware of the consequences thereby involved [146,245,259]. The following explanations describe the aspects to be considered in the interpretation of results. However, they specifically do not refer to a (possibly conclusive) assessment of benefit and harm by means of composite outcomes, if, for example, the potential harm from an intervention (e.g. increase in severe bleeding events) is included in an outcome together with the benefit (e.g. decrease in the rate of myocardial infarctions).

A precondition for consideration of a composite outcome is that the individual components of the composite outcome all represent patient-relevant outcomes defined in the report plan. In this context surrogate endpoints can be only included if they are specifically accepted by the Institute as valid (see Section 3.1.2). The results for every individual event included in a composite outcome should also be reported separately. The components should be of similar severity; this does not mean that they must be of identical relevance. For example, the outcome

[64] Risk of Bias in Non-randomized Studies - of Interventions

[65] Quality Assessment of Diagnostic Accuracy Studies

[66] Prediction Model Risk Of Bias Assessment Tool

"mortality" can be combined with "myocardial infarction" or "stroke", but not with "silent myocardial infarction" or "hospital admission".

If a composite outcome fulfils the preconditions stated above, then the following aspects need to be considered in the interpretation of conclusions on benefit and harm:

- Does the effect of the intervention on the individual components of the composite outcome usually take the same direction?
- Was a relevant outcome suited to be included in the composite outcome not included, or excluded, without a comprehensible and acceptable justification?
- Was the composite outcome defined a priori or introduced post hoc?

Insofar as the available data and data structures allow, sensitivity analyses may be performed by comparing the exclusion versus the inclusion of individual components.

If the relevant preconditions are fulfilled, individual outcomes may be determined and calculated from a composite outcome within the framework of a benefit assessment.

9.1.6 Assessment of data consistency

To assess the informative value of study results, the Institute will review the consistency of data with regard to their plausibility and completeness. On the one hand, implausible data are produced by the incorrect reporting of results (typing, formatting, or calculation errors), and on the other hand, by the insufficient or incorrect description of the methodology, or even by forged or invented data [13]. Inconsistencies may exist within a publication, and also between publications on the same study.

One problem with many publications is the reporting of incomplete information in the methods and results sections. In particular, the reporting of lost-to-follow-up patients, withdrawals, etc., as well as the way these patients were considered in the analyses, are often not transparent.

It is therefore necessary to expose potential inconsistencies in the data. For this purpose, the Institute reviews, for example, calculation steps taken, and compares data presented in text, tables, and graphs. In practice, a common problem in survival-time analyses arises from inconsistencies between the data on lost-to-follow-up patients and those on patients at risk in the survival curve graphs. For certain outcomes (e.g. total mortality), the number of lost-to-follow-up patients can be calculated if the Kaplan-Meier estimates are compared with the patients at risk at a point in time before the minimum follow-up time. Statistical techniques may be useful in exposing forged and invented data [13].

If relevant inconsistencies are found in the reporting of results, the Institute's aim is to clarify these inconsistencies and/or obtain any missing information by contacting authors, for example, or requesting the complete clinical study report and further study documentation. However, it should be considered that firstly, enquiries to authors often remain unanswered, especially

concerning older publications, and that secondly, authors' responses may produce further inconsistencies. In the individual case, a weighing-up of the effort involved and the benefit of such enquiries is therefore meaningful and necessary. If inconsistencies cannot be resolved, the potential impact of these inconsistencies on effect sizes (magnitude of bias), uncertainty of results (increase in error probability), and precision (width of the confidence intervals) will be assessed by the Institute. For this purpose, sensitivity analyses may be conducted. If it is possible that inconsistencies may have a relevant impact on the results, this will be stated and the results will be interpreted very cautiously.

9.2 Consideration of systematic reviews

9.2.1 Classification of systematic reviews

Relying on individual scientific studies can be misleading. Looking at one or only a few studies in isolation from other similar studies on the same question can make treatments appear more or less useful than they actually are. High-quality systematic reviews aim to overcome this form of bias by identifying, assessing and summarizing the evidence systematically, reproducibly and transparently, rather than selectively [196,211,280,557].

Systematic reviews identify, assess and summarize the evidence from one or several study types that can provide the best answer to a specific and clearly formulated question. Systematic and explicit methods are used to identify, select and critically assess the relevant studies for the question of interest. If studies are identified, these data are systematically extracted and analysed. Systematic reviews are non-experimental studies whose methodology must aim to minimize systematic errors (bias) on every level of the review process [211,351].

For systematic reviews of the effects of medical interventions, RCTs provide the most reliable answers. However, for other questions such as aetiology, prognosis or the qualitative description of patients' experiences, the appropriate evidence base for a systematic review will consist of other primary study types [280]. Systematic reviews of diagnostic and screening tests also show some methodological differences compared with reviews of treatment interventions [159].

For the work of the Institute, systematic reviews are mostly used to identify potentially relevant (primary) studies. However, an assessment can be based partially or even solely on systematic reviews (see Section 9.2.2). Health information produced by the Institute for patients and consumers is to a large part based on systematic reviews. These include, in particular, systematic reviews of treatment effects, causes of disease or prognostic factors. Syntheses of qualitative research are also used (see Section 9.4).

The minimal prerequisite for a systematic review on the effects of treatments to be used by the Institute is that it has only minimal methodological flaws according to the Oxman and Guyatt index [399,545,547], the AMSTAR [646-648], AMSTAR-2 [649] or the ROBIS[67] instrument

[67] Risk of Bias in Systematic Reviews

[749]. In addition to considering the strength of evidence investigated in systematic reviews, the Institute will also consider the relevance and applicability of the evidence. This includes investigating the question as to whether the results have been consistent among different populations and subgroups as well as in different health care contexts. The following factors are usually considered: the population of the participants in the included studies (including gender and baseline disease risk); the health care context (including the health care settings and the medical service providers); and the applicability and likely acceptance of the intervention in the form in which it was assessed [64,156].

9.2.2 Benefit assessment on the basis of systematic reviews

A benefit assessment on the basis of systematic reviews can provide a resource-saving and reliable evidence base for recommendations to the G-BA or the Federal Ministry of Health, provided that specific preconditions have been fulfilled [147,452]. In order to use systematic reviews in a benefit assessment these reviews must be of sufficiently high quality, that is, they must

- show only a minimum risk of bias
- present the evidence base in a complete, transparent, and reproducible manner

and thus allow clear conclusions to be drawn [28,545,752]. In addition, it is an essential prerequisite that the information retrieval conducted in the systematic reviews does not contradict the Institute's methodology (see Section 8.2.1) and that it is possible to transfer the results to the research question of the Institute's report, taking the defined inclusion and exclusion criteria into account.

The methodology applied must provide sufficient certainty that a new benefit assessment based on primary literature would not reach different conclusions from one based on systematic reviews. For example, this is usually not the case if a relevant amount of previously unpublished data is to be expected.

A) Research questions

In principle, this method is suited for all research questions insofar as the criteria named above have been fulfilled. The following points should be given particular consideration in the development of the research question:

- definition of the population of interest
- definition of the test intervention and comparator intervention of interest
- definition of all relevant outcomes
- if appropriate, specification of the health care setting or region affected (e.g. Germany, Europe)

The research question defined in this way also forms the basis for the specification of the inclusion and exclusion criteria to be applied in the benefit assessment, and subsequently for the specification of the relevance of the content and methods of the publications identified. On the basis of the research question, it is also decided which type of primary study the systematic reviews must be based on. Depending on the research question, it is possible that questions concerning certain parts of a commission are answered by means of systematic reviews, whereas primary studies are considered for other parts.

B) Minimum number of relevant systematic reviews

All systematic reviews that are of sufficient quality and relevant to the topic are considered. In order to be able to assess the consistency of results, at least 2 high-quality publications (produced independently of each other) should as a rule be available as the foundation of a report based on systematic reviews. If only one high-quality publication is available and can be considered, then it is necessary to justify the conduct of an assessment based only on this one systematic review.

C) Quality assessment of publications, including minimum requirements

The assessment of the general quality of systematic reviews is performed with Oxman and Guyatt's validated quality index for systematic reviews [544,545,547] or with the AMSTAR [646-648], AMSTAR-2 [649] or the ROBIS instrument [749]. According to Oxman and Guyatt's index, systematic reviews are regarded to be of sufficient quality if they have been awarded at least 5 of 7 possible points in the overall assessment, which is performed by 2 reviewers independently of one another. No such thresholds are defined for the AMSTAR, AMSTAR-2 or the ROBIS instrument and therefore should, if appropriate, be defined beforehand. In addition, as a rule, the sponsors of systematic reviews, as well as relationships of authors, are documented and discussed. Depending on the requirements of the project, the particular index criteria can be supplemented by additional items (e.g. completeness of the search, search for unpublished studies, for example in registries, or additional aspects regarding systematic reviews of diagnostic accuracy studies).

D) Results

For each research question, the results of a benefit assessment based on systematic reviews are summarized in tables, where possible. If inconsistent results on the same outcome are evident in several publications, possible explanations for this heterogeneity are described [398].

If the compilation of systematic reviews on a topic indicates that a new benefit assessment on the basis of primary studies could produce different results, then such an assessment will be performed.

E) Conclusion / recommendations

Benefit assessments based on systematic reviews summarize the results of the underlying systematic reviews and, if necessary, they are supplemented by a summary of up-to-date

primary studies (or primary studies on questions not covered by the systematic reviews). Independent conclusions are then drawn from these materials.

The recommendations made on the basis of systematic reviews are not founded on a summary of the recommendations or conclusions of the underlying systematic reviews. In HTA reports, they are often formulated against the background of the specific socio-political and economic setting of a particular health care system, and are therefore rarely transferable to the health care setting in Germany.

9.2.3 Consideration of published meta-analyses

Following international EBM standards, the Institute's assessments are normally based on comprehensive information retrieval for relevant primary studies, which is specific to the research question posed. If it is indicated and possible, results from individual studies identified are summarized and evaluated by means of meta-analyses. However, the Institute usually has access only to aggregated data from primary studies, which are extracted from the corresponding publication or the clinical study report provided. Situations exist where meta-analyses conducted on the basis of individual patient data (IPD) from relevant studies have a higher value (see Section 9.3.7). This is especially the case if, in addition to the effect caused solely by the intervention, the evaluation of other factors possibly influencing the intervention effect is also of interest (interaction between intervention effect and covariables). In this context, meta-analyses including IPD generally provide greater certainty of results, i.e. more precise results not affected by ecological bias, when compared with meta-regressions based on aggregated data [658]. In individual cases, these analyses may lead to more precise conclusions, particularly if heterogeneous results exist that can possibly be ascribed to different patient characteristics. However, one can only assume a higher validity of meta-analyses based on IPD if such analyses are actually targeted towards the research question of the Institute's assessment and also show a high certainty of results. The prerequisite for the assessment of the certainty of results of such analyses is maximum transparency; this refers both to the planning and to the conduct of analyses. Generally valid aspects that are relevant for the conduct of meta-analyses are outlined, for example, in the PRISMA statement on meta-analyses of randomized trials [549] and in the corresponding explanatory document [550], in the PRISMA-IPD statement for meta-analyses with IPD [680], in the PRISMA-P statement for protocols of systematic reviews [508] and in the corresponding explanatory document [645], in the PRISMA harms checklist, [771], the PRISMA-DTA statement for meta-analyses of diagnostic test accuracy studies [503], as well as in in a document published by EMA [223]. In its benefit assessments, the Institute considers published meta-analyses based on IPD if they address (sub)questions in the Institute's reports that cannot be answered with sufficient certainty by meta-analyses based on aggregated data. In addition, high certainty of results for the particular analysis is required.

9.3 Specific statistical aspects

9.3.1 Description of effects and risks

The description of intervention or exposure effects needs to be clearly linked to an explicit outcome variable. Consideration of an alternative outcome variable also alters the description and size of a possible effect. The choice of an appropriate effect measure depends in principle on the measurement scale of the outcome variable in question. For continuous variables, effects can usually be described using mean values and differences in mean values (if appropriate, after appropriate weighting). For categorical outcome variables, the usual effect and risk measures of 2x2 tables apply [45]. Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* [161] provides a well-structured summary of the advantages and disadvantages of typical effect measures in systematic reviews. Agresti [10,11] describes the specific aspects to be considered for ordinal data.

It is essential to describe the degree of statistical uncertainty for every effect estimate. For this purpose, the calculation of the standard error and the presentation of a confidence interval are methods frequently applied. Whenever possible, the Institute will state appropriate confidence intervals for effect estimates, including information on whether one- or two-sided confidence limits apply, and on the confidence level chosen. In medical research, the two-sided 95% confidence level is typically applied; in some situations, 90% or 99% levels are used. Altman et al. [19] give an overview of the most common calculation methods for confidence intervals.

In order to comply with the confidence level, the application of exact methods for the interval estimation of effects and risks should be considered, depending on the particular data situation (e.g. very small samples) and the research question posed. Agresti [12] provides an up-to-date discussion on exact methods.

9.3.2 Evaluation of statistical significance

With the help of statistical significance tests it is possible to test hypotheses formulated a priori with control for type 1 error probability. The convention of speaking of a “statistically significant result” when the p-value is lower than the significance level of 0.05 ($p < 0.05$) may often be meaningful. Depending on the research question posed and hypothesis formulated, a lower significance level may be required. Conversely, there are situations where a higher significance level is acceptable. The Institute will always explicitly justify such exceptions.

A range of aspects should be considered when interpreting p-values. It must be absolutely clear which research question and data situation the significance level refers to, and how the statistical hypothesis is formulated. In particular, it should be evident whether a one- or two-sided hypothesis applies [61] and whether the hypothesis tested is to be regarded as part of a multiple hypothesis testing problem [713]. Both aspects, whether a one- or two-sided hypothesis is to be formulated, and whether adjustments for multiple testing need to be made, are a matter of repeated controversy in scientific literature [240,430].

Regarding the hypothesis formulation, a two-sided test problem is traditionally assumed. Exceptions include non-inferiority studies. The formulation of a one-sided hypothesis problem is in principle always possible, but requires precise justification. In the case of a one-sided hypothesis formulation, the application of one-sided significance tests and the calculation of one-sided confidence limits are appropriate. For better comparability with two-sided statistical methods, some guidelines for clinical trials require that the typical significance level should be halved from 5% to 2.5% [371]. The Institute generally follows this approach. The Institute furthermore follows the central principle that the hypothesis formulation (one- or two-sided) and the significance level must be specified clearly a priori. In addition, the Institute will justify deviations from the usual specifications (one-sided instead of two-sided hypothesis formulation; significance level unequal to 5%, etc.) or consider the relevant explanations in the primary literature.

If the hypothesis investigated clearly forms part of a multiple hypothesis problem, appropriate adjustment for multiple testing is required if the type I error is to be controlled for the whole multiple hypothesis problem [53]. The problem of multiplicity cannot be solved completely in systematic reviews, but should at least be considered in the interpretation of results [48]. If meaningful and possible, the Institute will apply methods to adjust for multiple testing. In its benefit assessments (see Section 3.1). The Institute attempts to control type I errors separately for the conclusions on every single benefit outcome. A summarizing evaluation is not usually conducted in a quantitative manner, so that formal methods for adjustment for multiple testing cannot be applied here either.

The Institute does not evaluate a statistically non-significant finding as evidence of the absence of an effect (absence or equivalence) [17]. For the demonstration of equivalence, the Institute will apply appropriate methods for equivalence hypotheses.

In principle, Bayesian methods may be regarded as an alternative to statistical significance tests [670,671]. Depending on the research question posed, the Institute will, where necessary, also apply Bayesian methods (e.g. for indirect comparisons, see Section 9.3.8).

9.3.3 Evaluation of clinical relevance

The term “clinical relevance” refers to different concepts in the literature. On the one hand, at a group level, it may address the question as to whether a difference between 2 treatment alternatives for a patient-relevant outcome (e.g. serious adverse effects) is large enough to recommend the general use of the better alternative. On the other hand, clinical relevance is understood to be the question as to whether a change (e.g. the observed difference of 1 point on a symptom scale) is relevant for individual patients. Insofar as the second concept leads to the inspection of group differences in the sense of a responder definition and corresponding responder analyses, both concepts are relevant for the Institute’s assessments.

In general, the evaluation of the clinical relevance of group differences plays a particular role within the framework of systematic reviews and meta-analyses, as they often achieve the power

to “statistically detect” the most minor effects [725]. In this context, in principle, the clinical relevance of an effect or risk cannot be derived from a p-value. Statistical significance is a statement of probability, which is not only influenced by the size of a possible effect but also by data variability and sample size. When interpreting the relevance of p-values, particularly the sample size of the underlying study needs to be taken into account [591]. In a small study, a very small p-value can only be expected if the effect is marked, whereas in a large study, highly significant results are not uncommon, even if the effect is extremely small [239,367]. Consequently, the clinical relevance of a study result can by no means be derived from a p-value.

Widely accepted methodological procedures for evaluating the clinical relevance of study results do not yet exist, regardless of which of the above-mentioned concepts are being addressed. For example, only a few guidelines contain information on the definition of relevant or irrelevant differences between groups [449,701]. Methodological manuals on the preparation of systematic reviews also generally provide no guidance or no clear guidance on the evaluation of clinical relevance at a system or individual level (e.g. the *Cochrane Handbook* [351]). However, various approaches exist for evaluating the clinical relevance of study results. For example, the observed difference (effect estimate and the corresponding confidence interval) can be assessed solely on the basis of medical expertise without using predefined thresholds. Alternatively, it can be required as a formal relevance criterion that the confidence interval must lie above a certain “irrelevance threshold” to exclude a clearly irrelevant effect with sufficient certainty. This then corresponds to the application of a statistical test with a shifting of the null hypothesis in order to statistically demonstrate clinically relevant effects [759]. A further proposal plans to evaluate relevance solely on the basis of the effect estimate (compared to a relevance threshold), provided that there is a statistically significant difference between the intervention groups [425]. In contrast to the use of a statistical test with a shifting of the null hypothesis, the probability of a type 1 error cannot be controlled thorough the evaluation of relevance by means of the effect estimate. Moreover, this approach may be less efficient. Finally, a further option in the evaluation of relevance is to formulate a relevance criterion individually, e.g. in terms of a responder definition [426]. In this context there are also approaches in which the response criterion within a study differs between the investigated participants by defining individual therapy goals a priori [583].

Patient-relevant outcomes can also be recorded by means of (complex) scales. A prerequisite for the consideration of such outcomes is the use of validated or established instruments. In the assessment of patient-relevant outcomes that have been operationalized by using (complex) scales, in addition to evaluating the statistical significance of effects, it is particularly important to evaluate the relevance of the observed effects of the interventions under investigation. This is required because the complexity of the scales often makes a meaningful interpretation of minor differences difficult. It therefore concerns the issue as to whether the observed difference between 2 groups is at all tangible to patients. This evaluation of relevance can be made on the basis of differences in mean values as well as responder analyses [635]. A main problem in the

evaluation of relevance is the fact that scale-specific relevance criteria are not defined or that appropriate analyses on the basis of such relevance criteria (e.g. responder analyses) are lacking [511]. Which approach can be chosen in the Institute's assessments depends on the availability of data from the primary studies.

In recent years, responder analyses based on a response criterion in terms of an individual minimally important difference (MID) have been increasingly conducted. However, the methodological problems of this approach are becoming increasingly apparent.

In principle, empirical methods that determine an MID using patient-reported anchors are preferred for determining MIDs; in addition, distribution-based methods are also used [543,576]. Systematic compilations of empirically determined MIDs show that a large number of MIDs are often published for individual measurement instruments, which can range widely within an instrument [123,127,315,531]. This variability may be due, among other things, to the fact that studies on determining MIDs use different anchors, observation periods or analytical methods [179,531,543]. There is currently no established standard that can be used to assess the quality of these studies and to estimate the informative value of the MIDs determined [123,179,408]. A first proposal for a quality assessment instrument of studies on determining MIDs and on the informative value of MIDs was published in 2020 [178]. Comprehensive results on applicability are still pending. However, a study on the reliability of this new instrument shows that in publications of studies on determining MIDs, essential parts of the methodology or the criteria for an assessment are mostly not reported at all [178]. Thus, an empirically determined MID for benefit assessments based on methodological quality criteria cannot be selected at present [177,179,408].

In addition to the methodological factors influencing the magnitude of the MIDs determined, another part of the variability of MIDs is caused by the fact that they depend on characteristics of the patient population in which the instrument is used and other contextual factors. For example, the severity of the disease, the type of intervention used, or the question as to whether patients experience an improvement or deterioration of their condition, may all influence the MID [14]. How to deal with this part of the variability of MIDs remains unresolved in the international discussion.

Against this background, the procedure described below is applied to ensure that suitable response thresholds are used in responder analyses within the framework of benefit assessments. On the one hand, the aim is to ensure that a response threshold reflects changes that are perceptible to patients with sufficient certainty. This response threshold is intended to represent a relatively small change, but the value may well be above a minimum threshold. This property also takes into account the empirical variability of MIDs and helps to ensure that the response criterion does not fall below the MIDs too frequently in different constellations. At the same time, selective outcome reporting is to be minimized, which could arise, for example, by selecting any one of many possible MIDs.

To develop an approach for the use of MIDs in benefit assessments, systematic reviews on MIDs were systematically identified in a bibliographic search [15,189,208,315,403,531,543,672]. These systematically compiled MIDs were related to the range of the respective scales. This approach identified a value of 15% of the range of the respective scales as a plausible threshold for a relatively small, but sufficiently certain noticeable change [381]. This as a rule results in the following approach:

1) If responder analyses using an MID are pre-specified in a study and the response criterion corresponds to **at least** 15% of the scale range of the measurement instrument used, these responder analyses are used for the assessment without further examination of the response criterion.
2) If pre-specified response criteria in terms of an MID are below 15% of the scale range, these are as a rule not used. In these cases and in those cases where no response criteria have been pre-specified at all, but analyses of continuous data are available instead, there are various possibilities. Either the analyses of continuous data can be used, in which case a general statistical measure is drawn upon in the form of standardized mean differences (SMD expressed as Hedges' g). In this context, an irrelevance threshold of 0.2 is used: If the confidence interval corresponding to the effect estimate lies completely above this irrelevance threshold, it is assumed that the effect size does not lie within a range that is certainly irrelevant. This is to ensure that the effect can be regarded at least as "small" with sufficient certainty [236]. Alternatively, analyses specified post hoc with a response criterion of **exactly** 15% of the scale range can be considered.
3) If both suitable responder analyses (response criterion pre-specified at least 15% of the scale range or exactly 15% of the scale range post hoc) and analyses of continuous data are available, the responder analyses are used.

9.3.4 Demonstration of a difference

Various aspects need to be considered in the empirical demonstration that certain groups differ with regard to a certain characteristic. It should first be noted that a demonstration (of a difference) should not be understood as proof in a mathematical sense. With the help of empirical study data, statements can only be made by allowing for certain probabilities of error. By applying statistical methods, these probabilities of error can, however, be specifically controlled and minimized in order to statistically demonstrate a hypothesis. A typical method for such a statistical demonstration in medical research is the application of significance tests. This level of argumentation should be distinguished from the evaluation of the clinical relevance of a difference. In practice, the combination of both arguments provides an adequate description of a difference based on empirical data.

When applying a significance test to demonstrate a difference, the research question should be specified a priori, and the outcome variable, the effect measure, and the statistical hypothesis formulation should also be specified on the basis of this question. It is necessary to calculate the sample size required before the start of the study, so that the study is large enough for a

difference to be detected. In simple situations, in addition to the above information, a statement on the clinically relevant difference should be provided, as well as an estimate of the variability of the outcome measure. For more complex designs or research questions, further details are required (e.g. correlation structure, recruitment scheme, estimate of drop-out numbers) [62,167].

Finally, the reporting of results should include the following details: the significance level for a statement; a confidence interval for the effect measure chosen (calculated with appropriate methods); descriptive information on further effect measures to explain different aspects of the results; as well as a discussion on the clinical relevance of the results, which should be based on the evaluation of patient-relevant outcomes.

9.3.5 Demonstration of equivalence

One of the most common serious errors in the interpretation of medical data is to rate the non-significant result of a traditional significance test as evidence that the null hypothesis is true [17]. To demonstrate "equivalence", methods to test equivalence hypotheses need to be applied [409]. In this context, it is important to understand that demonstrating exact "equivalence" (e.g. that the difference in mean values between 2 groups is exactly zero) is not possible by means of statistical methods. In practice, it is not demonstration of exact equivalence that is required, but rather demonstration of a difference between 2 groups that is "at most irrelevant". To achieve this objective, it must, of course, first be defined what an irrelevant difference is, i.e. an equivalence range must be specified.

To draw meaningful conclusions on equivalence, the research question and the resulting outcome variable, effect measure, and statistical hypothesis formulation need to be specified a priori (similar to the demonstration of a difference). In addition, in equivalence studies the equivalence range must be clearly defined. This range can be two-sided, resulting in an equivalence interval, or one-sided in terms of an "at most irrelevant difference" or "at most irrelevant inferiority". The latter is referred to as a "non-inferiority hypothesis" [151,371,585].

As in superiority studies, it is also necessary to calculate the required sample size in equivalence studies before the start of the study. The appropriate method depends on the precise hypothesis, as well as on the analytical method chosen [584].

Specifically developed methods should be applied to analyse data from equivalence studies. The confidence interval approach is a frequently used technique. If the confidence interval calculated lies completely within the equivalence range defined a priori, then this will be classified as the demonstration of equivalence. To maintain the level of $\alpha = 0.05$, it is sufficient to calculate a 90% confidence interval [409]. However, following the international approach, the Institute generally uses 95% confidence intervals.

Compared with superiority studies, equivalence studies show specific methodological problems. On the one hand, it is often difficult to provide meaningful definitions of equivalence

ranges [449]; on the other hand, the usual study design criteria, such as randomization and blinding, no longer sufficiently protect from bias [641]. Even without knowledge of the treatment group, it is possible, for example, to shift the treatment differences to zero and hence in the direction of the desired alternative hypothesis. Moreover, the ITT principle should be applied carefully, as its inappropriate use may falsely indicate equivalence [409]. For this reason, particular caution is necessary in the evaluation of equivalence studies.

9.3.6 Adjustment principles and multi-factorial methods

Primarily in non-randomized studies, multi-factorial methods that enable confounder effects to be compensated play a key role [420]. Studies investigating several interventions are a further important field of application for these methods [499]. In the medical literature, the reporting of results obtained with multi-factorial methods is unfortunately often insufficient [50,517]. To be able to assess the quality of such an analysis, the description of essential aspects of the statistical model formation is necessary [321,594], as well as information on the quality of the model chosen (goodness of fit) [362]. The most relevant information for this purpose is usually

- a clear description and a-priori specification of the outcome variables and all potential explanatory variables
- information on the measurement scale and on the coding of all variables
- information on the selection of variables and on any interactions
- information on how the assumptions of the model were verified
- information on the goodness of fit of the model
- inclusion of a table with the most relevant results (parameter estimate, standard error, confidence interval) for all explanatory variables

Depending on the research question posed, this information is of varying relevance. If it concerns a good prediction of the outcome variable within the framework of a prognosis model, a high-quality model is more important than in a comparison of groups, where an adjustment for important confounders must be made.

Inadequate reporting of the results obtained with multi-factorial methods is especially critical if the (inadequately described) statistical modelling leads to a shift of effects to the “desired” range, which is not recognizable with mono-factorial methods. Detailed comments on the requirements for the use of multi-factorial methods can be found in various reviews and guidelines [34,51,420].

The Institute uses common methods in its own regression analysis calculations [320]. In this context, results of multi-factorial models that were obtained from a selection process of variables should be interpreted with great caution. When choosing a model, if such selection processes cannot be avoided, a type of backward elimination will be used, as this procedure is preferable to the procedure of forward selection [320,686]. A well-informed and careful

preselection of the candidate predictor variable is essential in this regard [162]. For the modelling of continuous covariates, the Institute will, if necessary, draw upon flexible modelling approaches (e.g. regression using fractional polynomials [595,622]) to enable the appropriate description of non-monotonous associations.

9.3.7 Meta-analyses

A) General comments

Terms used in the literature, such as literature review, systematic review, meta-analysis, pooled analysis, or research synthesis, are often defined differently and not clearly distinguished [211]. The Institute uses the following terms and definitions:

- A non-systematic review is the assessment and reporting of study results on a defined topic, without a sufficiently systematic and reproducible method for identifying relevant research results on this topic. A quantitative summary of data from several studies is referred to as a pooled analysis. Due to the lack of a systematic approach and the inherent subjective component, reviews and analyses not based on a systematic literature search are extremely prone to bias.
- A systematic review is based on a comprehensive, systematic approach and assessment of studies, which is applied to minimize potential sources of bias. A systematic review may, but does not necessarily have to, contain a quantitative summary of study results.
- A meta-analysis is a statistical summary of the results of several studies within the framework of a systematic review. In most cases this analysis is based on aggregated study data from publications. An overall effect is calculated – if meaningful – from the effect sizes measured in individual studies, taking sample sizes and variances into account.
- More efficient analysis procedures are possible if IPD are available from the studies considered. An IPD meta-analysis is the analysis of data on the patient level within the framework of a general statistical model of fixed or random effects, in which the study is considered as an effect and not as an experimental unit.
- The Institute sees a prospective meta-analysis as a statistical summary (planned a priori) of the results of several prospective studies that were jointly planned. However, if other studies are available on the particular research question, these must also be considered in the analysis in order to preserve the character of a systematic review.

The usual presentation of the results of a meta-analysis is made by means of forest plots in which the effect estimates of individual studies and the overall effect (including confidence intervals) are presented graphically [461]. On the one hand, models with a fixed effect are applied, which provide weighted mean values of the effect sizes (e.g. weighting by inversing the variance). On the other hand, random-effects models are frequently chosen in which an estimate of the variance between individual studies (heterogeneity) is considered. The question as to which model should be applied in which situation has long been a matter of controversy

[216,642,733]. If information is available that the effects of the individual studies are homogeneous, a meta-analysis assuming a fixed effect is sufficient. However, such information will often not be available, so that in order to evaluate studies in their totality, an assumption of random effects is useful [644]. Moreover, it should be noted that the confidence intervals calculated from a fixed-effect model may show a substantially lower coverage probability with regard to the expected overall effect, even if minor heterogeneity exists when compared with confidence intervals from a random-effects model [85,286]. If the existence of heterogeneity cannot be excluded with sufficient certainty, a random-effects model should be chosen. Several methods exist for the conduct of meta-analyses with random effects [729].

According to recommendations from the literature, if a sufficient number of studies are available, as a rule the Knapp-Hartung method [328,428] should be used to conduct meta-analyses with random effects; in this context, the heterogeneity parameter is estimated using the Paule-Mandel method [387,728,730].

When using the Knapp-Hartung method for meta-analyses with random effects, it should be noted that in homogeneous data situations, misleadingly narrow confidence intervals can occur [590]. To avoid this, Knapp and Hartung [428] proposed an ad-hoc variance correction. According to recommendations in the literature, when the Knapp-Hartung method is applied, sensitivity analyses should always be performed using the fixed-effect model or the DerSimonian-Laird method [164] to investigate whether the use of the ad-hoc variance correction is appropriate [394,756]. If the confidence interval using the Knapp-Hartung method is narrower than that of the DerSimonian-Laird method, the Knapp-Hartung method with ad-hoc variance correction should be applied.

However, the use of meta-analyses with random effects reaches its limits in the case of very few studies (fewer than 5). As heterogeneity then cannot be reliably estimated [349], the use of meta-analyses with random effects can lead to very broad confidence intervals that potentially no longer allow conclusions on the evidence base. Especially in the case of very few studies, a fixed-effect model or a qualitative summary (see Section 3.1.4) should be considered [49]. If there are no arguments against the use of a fixed-effect model, this model should be chosen, especially in the case of only 2 studies. If the use of the fixed effect model is not justifiable, it should be assessed whether a common effect estimate is meaningful or, otherwise, a qualitative summary can be made. To evaluate when a common effect estimate is meaningful, the Institute proceeds as follows. First, pooled effects are calculated according to the Knapp-Hartung method – with and without variance correction – and according to the DerSimonian-Laird method. It is checked whether the confidence interval according to Knapp-Hartung (without variance correction) is narrower than that according to DerSimonian-Laird. If this is the case, the Knapp-Hartung effect estimate with variance correction is used; if not, the one without variance correction is used. Subsequently, it is checked whether this effect estimate is informative. The estimate is considered informative if the confidence interval (of the common effect) is included in the union of the confidence intervals of the individual studies. If the effect estimate is informative, it is checked whether the result calculated by means of Knapp-Hartung

is congruent with the result according to DerSimonian-Laird with regard to the conclusion on statistical significance. In the case of congruence, a common effect estimate is considered meaningful and this effect estimate (according to Knapp-Hartung) is used for the final evaluation. Otherwise, a common effect estimate is not considered meaningful. In summary, an effect estimate is not meaningful if the effect estimate is not informative or if the result calculated by means of Knapp-Hartung is not congruent with the result according to DerSimonian-Laird with respect to the conclusion on statistical significance.

Depending on the context, alternative procedures for meta-analytical summarization could also be an option, such as Bayesian approaches [35,260,261,665] or methods from the area of generalized linear models [63,446,493,563,659]. For the selection of a suitable approach and for sensitivity analyses, several alternative methods have to be applied, especially in the case of meta-analyses with very few studies [300]. As described in the following text, the Institute will only perform a meta-analytical summary of strongly heterogeneous study results if the reasons for this heterogeneity are plausible and still justify such a summary.

B) Heterogeneity

Before a meta-analysis is conducted, it must first be considered whether the pooling of the studies investigated is in fact meaningful, as the studies must be comparable with regard to the research question posed. In addition, even in the case of comparability, the studies to be summarized will often show heterogeneous effects [348]. In this situation it is necessary to assess the heterogeneity of study results [281]. The existence of heterogeneity can be statistically tested; however, these tests usually show very low power [393,432]. In addition, it is also important to quantify the extent of heterogeneity. For this purpose, specific statistical methods are available, such as the I^2 measure [347]. Studies exist for this measure that allow a rough classification of heterogeneity, for example, into the categories “might not be important” (0 to 40%), “moderate” (30 to 60%), “substantial” (50 to 90%) and “considerable” (75 to 100%) heterogeneity [161]. If the heterogeneity of the studies is too large, the statistical pooling of the study results may not be meaningful [161]. The specification as to when heterogeneity is too large depends on the context. A pooling of data is usually dispensed with if the heterogeneity test yields a p-value of less than 0.05. In this context, the location of the effects also plays a role. If the individual studies show a clear conclusive effect, then pooling heterogeneous results by means of a random effects model can also lead to a conclusion on the benefit of an intervention. However, in this situation a positive conclusion on the benefit of an intervention may possibly be drawn without the quantitative pooling of data (see Section 3.1.4). In the other situations the Institute will not conduct a meta-analysis. However, not only statistical measures, but also reasons of content should be considered when making such a decision, which must be presented in a comprehensible way. In this context, the choice of the effect measure also plays a role. The choice of a certain measure may lead to great study heterogeneity, yet another measure may not. For binary data, relative effect measures are frequently more stable than absolute ones, as they do not depend so heavily on the baseline risk [263]. In such cases, the data analysis should be conducted with a relative effect measure, but

for the descriptive presentation of data, absolute measures for the specific baseline risks may possibly be inferred from relative ones (see Section 7.7).

In the case of great heterogeneity of the studies, it is necessary to investigate potential causes. Factors that could explain the heterogeneity of effect sizes may possibly be detected by means of meta-regression [703,722]. In a meta-regression, the statistical association between the effect sizes of individual studies and the study characteristics is investigated, so that study characteristics can possibly be identified that explain the different effect sizes, i.e. the heterogeneity. However, when interpreting results, it is important that the limitations of such analyses are taken into account. Even if a meta-regression is based on randomized studies, only evidence of an observed association can be inferred from this analysis, not a causal relationship [703]. Meta-regressions that attempt to show an association between the different effect sizes and the average patient characteristics in individual studies are especially difficult to interpret. These analyses are subject to the same limitations as the results of ecological studies in epidemiology [294]. Due to the high risk of bias, which in analyses based on aggregate data cannot be balanced by adjustment, definite conclusions are only possible on the basis of IPD [559,658,703] (see Section 9.2.3).

The Institute uses prediction intervals to display heterogeneity within the framework of a meta-analysis with random effects [299,349,580,728]. In contrast to the confidence interval, which quantifies the precision of an estimated effect, the 95% prediction interval covers the true effect of a single (new) study with a probability of 95%. In this context it is important to note that a prediction interval cannot be used to assess the statistical significance of an effect. The Institute follows the proposal by Guddat et al. [299] to insert the prediction interval – clearly distinguishable from the confidence interval – in the form of a rectangle in a forest plot. The use of meta-analyses with random effects and related prediction intervals in the event of very few studies (less than 5) is critically discussed in the literature, as potential heterogeneity can only be estimated very imprecisely [349,395]. The Institute generally presents prediction intervals in forest plots of meta-analyses with random effects if at least 5 studies are available and if the graphic display of heterogeneity is important, for example, to assess whether and to what extent the effects are conclusive (see Section 3.1.4).

If no pooled effect is displayed because heterogeneity is too large, prediction intervals are also used in order to evaluate whether the effects observed in the available studies are moderately or clearly conclusive (see Section 3.1.4). In this case, as a rule prediction intervals are used if at least 4 studies are available.

C) Small number of events

A common problem of meta-analyses using binary data is the existence of so-called “zero cells”, i.e. cases where not a single event was observed in an intervention group of a study. the Institute follows the usual approach here; i.e. in the event of zero cells, the correction value of 0.5 is added to each cell frequency of the corresponding fourfold table [161]. This approach is appropriate as long as not too many zero cells occur. In the case of a low overall number of

events, it may be necessary to use other methods. In the case of very rare events the Peto odds-ratio method can be applied; this does not require a correction term in the case of zero cells [76,161]. However, the use of this method is only adequate if the effects to be estimated are not too large and the design is not unbalanced [83,84].

If studies do exist in which no event is observed in either study arm (so-called "double-zero studies") then in practice these studies are often excluded from the meta-analytic calculation. This procedure should be avoided if too many double-zero studies exist. Several methods are available to avoid the exclusion of double-zero studies. The absolute risk difference may possibly be used as an effect measure which, especially in the case of very rare events, often does not lead to the heterogeneities that otherwise usually occur. Further potential methods comprise logistic regression models with random effects [659,715], beta-binomial models [446,493] exact methods [706] or the application of the arcsine difference [597]. Depending on the particular data situation, the Institute will select an appropriate method and, if applicable, examine the robustness of results by means of sensitivity analyses.

D) Meta-analyses of diagnostic accuracy studies

The results of diagnostic accuracy studies can also be statistically pooled by means of meta-analytic techniques [176,392,481]. However, as explained in Section 3.5, studies investigating only diagnostic accuracy are mostly of subordinate relevance in the evaluation of diagnostic tests, so that meta-analyses of diagnostic accuracy studies are likewise of limited relevance.

The same basic principles apply to a meta-analysis of diagnostic accuracy studies as to meta-analyses of therapy studies [176,572]. Here too, it is necessary to conduct a systematic review of the literature, assess the methodological quality of the primary studies, conduct sensitivity analyses, and examine the potential influence of publication bias.

In practice, in most cases heterogeneity can be expected in meta-analyses of diagnostic accuracy studies; therefore it is usually advisable here to apply random-effects models [176]. Such a meta-analytical pooling of diagnostic accuracy studies can be performed by means of separate models for sensitivity and specificity, if the evidence on the use of bivariate models is insufficient [696]. However, if a summarizing receiver operating characteristic (ROC) curve and/or a two-dimensional estimate for sensitivity and specificity are of interest, newer bivariate meta-analyses with random effects show advantages [316,573]. These methods also enable consideration of explanatory variables [314]. Meta-analytical methods have also been developed for complex data situations with several diagnostic thresholds at the study level [363,412,677]. Results are presented graphically either via the separate display of sensitivities and specificities in the form of modified forest plots or via a two-dimensional illustration of estimates for sensitivity and specificity. In analogy to the confidence and prediction intervals in meta-analyses of therapy studies, confidence and prediction regions can be presented in the ROC area in bivariate meta-analyses of test accuracy studies.

E) Cumulative meta-analyses

For some time it has been increasingly discussed whether, in the case of repeated updates of systematic reviews, one should calculate and present meta-analyses included in these reviews as cumulative meta-analyses with correction for multiple testing [67,86,87,532,704,746]. As a standard the Institute applies the usual type of meta-analyses and normally does not draw upon methods for cumulative meta-analyses.

However, if the conceivable case arises that the Institute is commissioned with the regular update of a systematic review to be updated until a decision can be made on the basis of a statistically significant result, the Institute will consider applying methods for cumulative meta-analyses with correction for multiple testing.

9.3.8 Indirect comparisons

Methods for indirect comparisons are understood to be both techniques for a simple indirect comparison of 2 interventions as well as techniques in which direct and indirect evidence are combined. The latter are called mixed treatment comparison (MTC) meta-analysis [473-475], multiple treatments meta-analysis (MTM) [117], or network meta-analysis [478,596,609]. These methods represent an important further development of the usual meta-analytic techniques [608]. However, there are still several unsolved methodological problems, so that currently the routine application of these methods within the framework of benefit assessments is not advisable [33,266,610,667,688]. For this reason, direct comparative studies are primarily used in benefit assessments of interventions (placebo-controlled studies as well as head-to-head comparisons); this means that conclusions for benefit assessments are preferably inferred from the results of direct comparative studies. Adequate justification is required if methods for indirect comparisons are to be used. In addition, an essential precondition for consideration of an indirect comparison is that it is targeted towards the overall research question of interest and not only towards selective components such as individual outcomes.

In certain situations, as, for example, in assessments of the benefit of drugs with new active ingredients [171], as well as in health economic evaluations (HEEs, see below), it can however be necessary to consider indirect comparisons and infer conclusions from them for the benefit assessment, taking a lower certainty of results into account.

For the HEE of interventions, conjoint quantitative comparisons of multiple (of more than 2) interventions are usually required. Limiting the study pool to direct head-to-head comparisons would mean limiting the HEE to a single pairwise comparison or even making it totally impossible. In order to enable an HEE of multiple interventions, it can be necessary to regularly consider indirect comparisons to assess cost-effectiveness ratios (see Chapter 4), taking into account the lower certainty of results compared with the approach of a pure benefit assessment.

However, appropriate methods for indirect comparisons need to be applied. The use of non-adjusted indirect comparisons (i.e. the use of single arms from different studies) is disapproved [54]. This also applies to methods for indirect comparisons in which, via modelling with strong

assumptions about unknown effects [122] or by means of methods from the area of causal models for observational studies with non-testable assumptions [656], it is attempted to enable estimations of effects despite missing common comparators. Only adjusted indirect comparisons via adequate common comparators are accepted. These particularly include the approach by Bucher et al. [101], as well as the network meta-analysis methods mentioned above.

Besides the assumptions of sufficient similarity and homogeneity of the pairwise meta-analyses, which must also be fulfilled here, in network meta-analyses sufficient consistency of the effects estimated from the direct and indirect evidence is additionally required. The latter is a critical point, as network meta-analyses provide valid results only if the consistency assumption is fulfilled. Several methods are available for examining the consistency assumption [181,194,475]. However, they have not yet been insufficiently investigated and no methodological standard has so far been established here [684]. In addition, consistency cannot always be examined, as a comparison of direct and indirect evidence is not possible (e.g. in the method following Bucher et al. [101]). In these cases in particular, a very careful evaluation of similarity and homogeneity is therefore required [424]. If serious doubts exist whether one or several of the basic assumptions are fulfilled to a sufficient extent, then indirect comparisons should not be used [423].. In practice it is necessary to describe completely the model applied, together with any remaining unclear issues [688]. These issues should be carefully examined in sensitivity analyses. The guidelines available in the literature on the conduct and assessment of indirect comparisons should be observed [6,354,369,400,401,423].

9.3.9 Subgroup analyses

With subgroup analyses it is examined whether the results of one or several studies differ between the different subgroups included in these studies (e.g. patient with versus patients without renal dysfunction). This difference can be qualitative (reversal of the effect in one subgroup, but not in another) or quantitative (different effect sizes).

Such subgroup analyses are useful for the targeted use of medical interventions, as with these analyses patient groups can potentially be defined for whom an intervention has a benefit or for whom the same intervention is more likely to be harmful than beneficial. This information can also lead to a restriction of the therapeutic indication of an intervention, for example in the approval of drugs. Even though subgroup analyses are useful for treatment optimization, they are in part a matter of controversy in the methodological literature [27,546].

- Lack of power: The sample size of a subgroup is often too small to enable the detection of moderate differences (by means of inferential statistics), so that even if effects actually exist, the result within a subgroup does not necessarily have to be statistically significant [287]. The situation is different if an adequate power for the subgroup analysis was already considered in the sample size calculation and a correspondingly larger sample size was planned [88].

- Multiple testing: If several subgroups are analysed, results in a subgroup may well reach statistical significance, despite actually being random.
- Comparability between treatment groups within the subgroups: If randomization was not stratified according to the subgroup characteristic, in the event of small sample sizes within the subgroups the treatment groups could differ with regard to prognostic factors [150,687]. In this case, the comparability between treatment groups within the subgroups is jeopardized, so that (non-) existing differences between subgroups can be caused by this imbalance alone.
- Effect modification through more than one subgroup characteristic (interaction of higher order): If for one outcome there is a difference, for example, between 2 age groups, as well as between men and women, to interpret the results separate analyses are required for each age group as well as for men and women (i.e. analyses of 4 subgroups). However, such analyses are rarely available.

Moreover, it is being discussed that subgroup analyses generally have no characteristic of proof, particularly if they were not planned a priori. If subgroup analyses with regard to more or less arbitrary subgroup-forming characteristics are conducted post hoc, their results cannot be regarded as a methodologically correct testing of a hypothesis. Whereas in general subgroup analyses conducted post hoc on a study level should be viewed critically (also in view of the methodological limitations named above), in a systematic review one still depends on the use of the results of such analyses on a study level if the review is supposed to investigate precisely these subgroups. Such subgroup analyses are not to be designated as “post hoc” in terms of the systematic review, but correspond to a hypothesis to be tested in this review. In this respect the analysis of heterogeneity between the individual studies (and thus potentially the analyses of subgroups) are a scientific necessity. Subgroup analyses of characteristics not recorded before randomization but during the course of the study (e.g. patients with versus patients without myocardial infarction under the treatment investigated) are as a matter of principle unreliable.

On the one hand the aspects mentioned above require the assessment of the credibility of subgroup analyses; Sun et al. [687] identified criteria for this purpose. On the other hand, despite these limitations, for some research questions subgroup analyses may represent the best scientific evidence available in the foreseeable future in order to assess effects in subgroups [257], since, for example, factors such as ethical considerations may argue against the verification of the observed findings in further studies.

Expected differences in effects between different, clearly distinguishable patient populations are an important reason for conducting subgroup analyses [438,589]. If a-priori information is available on a possible effect modifier (e.g. age, pathology), it is in fact essential to investigate possible heterogeneity in advance with regard to the effect in the various patient groups.

Subgroup analyses can also be a necessity from the perspective of social law: According to §139a (2) SGB V, the Institute is obliged to consider characteristics specific to age, gender, and

life circumstances. In addition, it should also be elaborated in which patient groups a new drug is expected to lead to a relevant improvement in treatment success, with the aim of providing these patients with access to this new drug [170]. A corresponding objective can also be found in §35a SGB V regarding the assessment of the benefit of drugs with new active ingredients [171]. In this assessment, patient groups should be identified in whom these drugs show a therapeutically relevant added benefit.

When interpreting subgroup analyses it should be considered that a statistically significant effect in one subgroup, but no effect or a reversed effect in another subgroup, cannot on its own (by means of inferential statistics) be interpreted as the existence of different effects between subgroups. Instead, first of all the statistical demonstration of different effects between different subgroups should be conducted by means of an appropriate homogeneity or interaction test. If a certain probability for such a demonstration is to exist at all, as a rule subgroup analyses are only conducted if each subgroup comprises at least 10 people and, in the event of binary data and survival times, at least 10 events occurred in one of the subgroups. An "event" means an event that occurred during the course of the observation period and was not detectable at baseline (e.g. achievement of viral clearance in infected persons).

If the result of a heterogeneity or interaction test between important subgroups is significant at the level of $\alpha = 0.05$, an effect modification (i.e. different effects between subgroups) is present. In this case the results of subgroups are not pooled to a common effect estimate. In the case of more than 2 subgroups, pairwise statistical tests to detect interactions are conducted, if meaningful. Pairs that are not statistically significant at the level of $\alpha = 0.05$ (with simultaneous statistical significance of the remaining pairs) are summarized into one group. The results of the remaining groups are reported separately and separate conclusions on the benefit of the intervention for these groups are inferred. If no pairs can be found that are not statistically significant at the level of $\alpha = 0.05$, no pairs are formed; instead a separate conclusion is drawn for each subgroup. In situations that are inconclusive on the basis of the pairwise interaction tests (e.g. when only a single pairwise interaction test is statistically significant), a decision is made on a case-by-case basis as to whether subgroup pairs should be combined into one group, and if so, which ones.

An exception to the requirement for an adequate homogeneity or interaction test exists if a necessity according to social law arises for subgroup analyses through the approval status of drugs. On the one hand, this may be the consequence of the decision by regulatory authorities that, after balancing the efficacy and risks of a drug, may determine that it will only be approved for part of the patient populations investigated in the approval studies. These considerations may also be based on subgroup analyses conducted post hoc. On the other hand, studies conducted after approval may include patient groups for whom the drug is not approved in Germany; the greater the differences between approvals on an international level, the more this applies. In such cases, subgroup analyses reflecting the approval status of a drug may need to be used, independently of whether these analyses were planned a priori within the study or not.

9.3.10 Handling of unpublished or partially published data

In the quality assessment of publications, in practice the problem frequently arises that essential data or information is partially or entirely missing (see Section 8.1). Moreover, it is possible that studies have not (yet) been published at the time of the Institute's technology assessment.

It is the Institute's aim to conduct an assessment on the basis of a data set that is as complete as possible. If relevant information is missing, the Institute therefore tries to complete the missing data, among other things by contacting the authors of publications or the study sponsors (see Sections 3.2.1 and 8.1.3). However, depending on the type of product prepared, requests for unpublished information may be restricted due to time limits.

A common problem is that important data required for the conduct of a meta-analysis (e.g. variances of effect estimates) are lacking. However, in many cases, missing data can be calculated or at least estimated from the data available [180,364,551]. If possible, the Institute will apply such procedures.

If data are only partly available or if estimated values are used, the robustness of results will be analysed and discussed, if appropriate with the support of sensitivity analyses (e.g. by presenting best-case and worst-case scenarios). However, a worst-case scenario can only be used here as proof of the robustness of a detected effect. From a worst-case scenario not confirming a previously found effect it cannot be concluded that this effect is not demonstrated. In cases where relevant information is largely or completely lacking, it may occur that a publication cannot be assessed or a study cannot be used in the analysis. In such cases, it will be noted that further data exist on a particular topic, but are not available for a quality assessment or for the analysis; this is accordingly taken into account in the assessment across studies (e.g. by downgrading the certainty of conclusions, see Section 3.2.1).

9.3.11 Handling of incomplete data

Whenever a study is followed up, it is inevitable that study participants will no longer be available for data collection on outcomes. These losses to follow-up can be due to a wide variety of reasons, e.g. death, study discontinuation or switch of intervention (by the doctor or patient), revocation of the informed consent due to side effects or lack of efficacy, newly occurring comorbidity or the stressful nature of the follow-up itself. The standards for reporting clinical trials stipulate that the reasons for losses to follow-up – if known – must be reported separately for each intervention group (see Section 9.1.1). Losses to follow-up, i.e. study participants who are included in the analyses with incomplete data, should be distinguished from study participants who were included in the study but are completely disregarded in the analyses (regardless of whether follow-up occurred, is complete, or is incomplete). For an intention-to-treat analysis, if possible, all randomized study participants should also be considered in the analysis [243].

Both losses to follow-up and study participants who remain completely unaccounted for in the analyses lead to missing data (partial or complete). Missing data not only increase the statistical uncertainty of the effect estimate, but also lead to a risk of bias unless it is clearly evident from the reasons for losses to follow-up or exclusions from the analyses that drop-outs were missing completely at random [469]. The risk of bias increases with an increasing proportion of missing values.

In addition to losses to follow-up, missing values can also occur sporadically or temporarily – even at baseline – and even if a study participant attends the study visit (e.g. loss of samples, technical failure or errors in the documentation of measurements). However, missing values due to such reasons are of minor importance in practice.

In a 2-step process, the missing values are assessed. In the first step, study participants who were completely excluded from the analyses are evaluated. Results are generally not included in the benefit assessment if they are based on less than 70% of the study participants to be included in the analysis, i.e., if the proportion of study participants not included in the analysis at all is greater than 30%. In some of the literature, analyses in which 20% of the study participants are not included are no longer considered meaningful [633]. Furthermore, the results are also not included in the benefit assessment if the difference in the proportions of study participants not included is greater than 15 percentage points between the groups, as this indicates non-random exclusion. Depending on the context, these rules are not rigid but should be viewed as guidance. Exceptions to these rules are made when exclusions are shown to be completely at random.

In the second step, the losses to follow-up are evaluated, i.e. the study participants included in the analyses but incompletely observed. No fixed limits are applied for the assessment of the risk of bias due to these losses. The extent of the risk of bias is determined, depending on the context, by the number, the time points as well as the reasons for the losses to follow-up. In particular, differences between groups in these factors increase the risk of bias. If the proportion of missing values is too high or inappropriate replacement strategies were used, the results may not be taken into account.

The results are considered robust if the potential problems due to losses to follow-up are compensated by adequate replacement strategies or statistical analysis methods [44,250]. For this, it is necessary to know in detail and be able to describe the mechanism that led to the missing data. This will be impossible in practice if the proportion of missing data is too high.

9.3.12 Handling of variable observation periods

If the entry time of patients differs in clinical studies (recruitment period), but the follow-up time point is identical, the result is that the observation periods for the individual patients are different. In order to take this adequately into account, methods of survival time analysis are available [427,455]. Commonly used standard methods are the Kaplan-Meier curve for estimating the survival function, the log-rank test for comparing multiple survival functions,

and the Cox model for estimating (adjusted) hazard ratios. When examining non-fatal outcomes (such as non-fatal myocardial infarction), it is important to note that death is always a competing event for non-fatal events. In this case, special methods of survival analysis for competing risks must be applied [31,416]. In this context, the application of the usual Kaplan-Meier curve leads to an overestimation of the absolute risk [448] and it should therefore not be used. Instead, the Aalen-Johansen estimator for the cumulative incidence function should be applied [628]. In contrast, the application of the Cox model for the cause-specific hazard function represents a correct analysis. However, for a complete analysis of all data, one also needs the Cox model for the competing event [628]. Another option is the application of the Fine-Gray model [247]; the corresponding explanations can be found in the literature [32,570].

Particularly when investigating adverse events and PROs in oncological studies, the additional problem often arises that they are only collected during treatment and that the corresponding observations are censored if treatment is discontinued or switched. This often results in different mean observation periods in the 2 groups to be compared. Although for the analysis of adverse events, the consideration of observation periods by using adequate survival time methods has long been demanded in drug approval [535,536], simple methods based on relative frequencies or incidence densities still dominate in this area [47,720].

In benefit assessments, however, analyses are required for all patient-relevant outcomes that allow conclusions to be drawn on the basis of adequate statistical inference. This means that adequate survival time methods are needed, especially in comparisons of groups with different mean observation periods [46,47]. If the reason for the different mean observation periods is incomplete data collection (censoring when treatment is discontinued or switched), the problem of informative censoring also arises when using survival time methods, which may result in a high risk of bias. To avoid such problems, data on adverse events should be collected completely, even after discontinuation or switching of treatment [47]. The frequently applied practice of recording adverse events only up to a maximum of 30 days after discontinuation or switching of treatment is insufficient for benefit assessments, since analyses based on the treatment policy estimand (i.e. an estimate of the effect for the entire treatment strategy independent of discontinuation or switching of treatment) and the intention-to-treat principle are required [47,767]. Survival time analyses are sometimes performed for PROs in the case of different observation periods (e.g. responder analyses for time to deterioration), but these analyses lack the medically necessary information on PROs after discontinuation or switching of treatment.

If the groups to be compared have observation periods of different lengths without adequate consideration in the data analysis, this may mean that the corresponding results cannot be used in the benefit assessment.

9.3.13 Description of types of bias

Bias is the systematic deviation of the effect estimate (inferred from study data) from the true effect. Bias may be produced by a wide range of possible causes [131]. The following text

describes only the most important types; a detailed overview of various types of bias in different situations is presented by Feinstein [238].

Selection bias is caused by a violation of the random principles for sampling procedures, i.e. in the allocation of patients to intervention groups. Particularly in the comparison of 2 groups, selection bias can lead to systematic differences between groups. If this leads to an unequal distribution of important confounders between groups, the results of a comparison are usually no longer interpretable. When comparing groups, randomization is the best method to avoid selection bias [350], as the groups formed do not differ systematically with regard to known as well as unknown confounders. However, structural equality can only be ensured if the sample sizes are sufficiently large. In small studies, despite randomization, relevant differences between groups can occur at random. When comparing groups with structural inequality, the effect of known confounders can be taken into account by applying multi-factorial methods. However, the problem remains of a systematic difference between the groups due to unknown or insufficiently investigated confounders.

Besides the comparability of groups with regard to potential prognostic factors, equality of treatment and equality of observation for all participants play a decisive role. Performance bias is bias caused by different types of care provided (apart from the intervention to be investigated). A violation of the equality of observation can lead to detection bias. Blinding is an effective protection against both performance and detection bias [414], which are summarized as information bias in epidemiology.

If not taken into account, protocol violations and study withdrawals can cause a systematic bias of study results, called attrition bias. To reduce the risk of attrition bias, in studies that aim to show superiority, the ITT principle can be applied, where all randomized study participants are analysed within the group to which they were randomly assigned, independently of protocol violations [414,442].

Missing values due to other causes present a similar problem. Missing values not due to a random mechanism can also cause bias in a result [469]. The possible causes and effects of missing values should therefore be discussed on a case-by-case basis and, if necessary, statistical methods should be applied to account or compensate for bias. In this context, replacement methods (imputation methods) for missing values are only one class of various methods available, of which none are regarded to be generally accepted. For example, EMA recommends comparison of various methods for handling missing values in sensitivity analyses [228].

When assessing screening programmes, it needs to be considered that earlier diagnosis of a disease often results only in an apparent increase in survival times, due to non-comparable starting points (lead time bias). Increased survival times may also appear to be indicated if a screening test preferably detects mild or slowly progressing early stages of a disease (length

bias). The conduct of a randomized trial to assess the effectiveness of a screening test can protect against these bias mechanisms [252].

Reporting bias is caused by the selective reporting of only part of all relevant data and may lead to an overestimation of the benefit of an intervention in systematic reviews. If, depending on the study results, some analyses or outcomes are not reported or reported in less detail within a publication, or reported in a way deviating from the way originally planned, then selective reporting bias or outcome reporting bias is present [130,203,284,285,548]. In contrast, publication bias describes the fact that studies finding a statistically significant negative difference or no statistically significant difference between the test intervention and control group are not published at all or published later than studies with positive and statistically significant results [75]. The pooling of published results can therefore result in a systematic bias of the common effect estimate. Graphic methods such as the funnel plot [212] and statistical methods such as meta-regression can be used to identify and consider publication bias. These methods can neither certainly confirm nor exclude the existence of publication bias, which underlines the importance of also searching for unpublished data.

In studies conducted to determine the accuracy of a diagnostic strategy (index test), results may be biased if the reference test does not correctly distinguish between healthy and sick participants (misclassification bias). If the reference test is only conducted in a non-random sample of participants receiving the index test (partial verification bias) or if the reference test applied depends on the result of the index test (differential verification bias), this may lead to biased estimates of diagnostic accuracy. Cases in which the index test itself is a component of the reference test may lead to overestimates of diagnostic accuracy (incorporation bias) [456].

Spectrum bias is a further type of bias mentioned in the international literature. This plays a role in studies where the sample for validation of a diagnostic test consists of persons who are already known to be sick and healthy volunteers as a control group [466]. The validation of a test in such studies often leads to estimates for sensitivity and specificity that are higher than they would be in a clinical situation where patients with a suspected disease are investigated [748]. However, the use of the term bias (in the sense of a systematic impairment of internal validity) in this connection is unfortunate, as the results of such studies may well be internally valid if the study is conducted appropriately [748]. Nonetheless, studies of the design described above may have features (particularly regarding the composition of samples) due to which they are not informative for clinical questions in terms of external validity.

As in intervention studies, in diagnostic studies it is necessary to completely consider all study participants (including those with unclear test results) in order to avoid systematic bias of results [456]. While numerous investigations are available on the relevance and handling of publication bias in connection with intervention studies, this problem has been far less researched for diagnostic accuracy studies [456].

A general problem in the estimation of effects is bias caused by measurement errors in the study data collected [124,132]. In practice, measurement errors can hardly be avoided and it is known that non-differential measurement errors can also lead to a biased effect estimate. In the case of a simple linear regression model with a classical measurement error in the explanatory variable, "dilution bias" occurs, i.e. a biased estimate in the direction of the zero effect. However, in other models and more complex situations, bias in all directions is possible. Depending on the research question, the strength of potential measurement errors should be discussed, and, if required, methods applied to adjust for bias caused by measurement errors.

9.3.14 Analysis of dependent data

Simple standard procedures of medical statistics assume independent experimental units within a treatment arm. In certain situations (e.g. in cluster-randomized studies or studies of eyes or teeth) in which several experimental units of a cluster or a patient within a treatment arm are included in the analysis, this independency does not apply. The application of simple standard procedures for independent experimental units within a treatment arm then leads to an underestimation of variance and possibly to incorrect conclusions on significance, as the p-values calculated are too small [18]. Evidence from studies that used simple standard procedures despite correlated data can potentially still be considered, if the related error can be properly classified. If this is not the case, then results from studies with correlated data cannot be interpreted adequately. In the event of dependent data within a treatment arm, then the related correlation structure must be considered by applying suitable methods for dependent data. In practice, the Generalized Estimating Equations [111] as well as methods from the class of mixed models [96] are commonly used methods.

Dependencies can also arise between the treatment arms to be compared (e.g. due to matching or in cross-over studies), which must be accounted for in the data analysis by applying appropriate statistical methods for paired samples or cross-over studies [410,643].

9.4 Qualitative methods

Qualitative research methods are applied to explore and understand subjective experiences, individual actions, and the social world [184,318,484,519]. They can, among other things, enable access to opinions and experiences of patients and their relatives with respect to a certain disease or intervention.

The instruments of qualitative research include focus groups conducted with participants of a randomized controlled trial, for example. Qualitative data can also be collected by means of interviews, observations, and written documents, such as diaries.

An analysis follows collection of data, which mainly aims to identify and analyse overlapping topics and concepts in the data collected. Among other things, qualitative methods can be used as an independent research method, in the preparation of or as a supplement to quantitative studies, within the framework of the triangulation or mixed-method approach, or after the

conduct of quantitative studies, in order to explain processes or results. Qualitative research is seen as a method to promote the connection between evidence and practice [186].

9.4.1 Qualitative research in the production of health information

In the development of health information, research findings from qualitative primary studies and reviews of qualitative studies are used to identify (potential) information needs, as well as to investigate patients' experiences with a certain disease or intervention and to investigate how they cope with a disease. In particular, the following questions should be answered:

- What questions do people have with regard to this disease/this topic?
- How do people perceive this disease/this intervention?
- When do people visit a doctor and how do they perceive their symptoms?
- What experiences, problems, challenges and questions do people have with regard to diagnostic procedures and the diagnosis?
- What experiences have people made with the treatment or the treatment decision?
- What experiences, problems, challenges and questions do people have with regard to coping with daily life?
- What information do people need?
- How can information support people (e.g. by the processing and format)?

For this purpose, focused information retrieval in bibliographic databases is conducted (see Section 8.2.2).

The study quality is assessed by means of criteria defined beforehand. In recent years various instruments for evaluating the quality of qualitative studies have been developed [153]. The assessment of qualitative studies aims to determine whether the study design, study quality, and reliability are appropriate for the research question investigated. No general consensus exists yet with regard to the criteria for the conduct, assessment, and synthesis of qualitative studies when compared with other research areas [184,187,318,519]. The Institute monitors the methodological developments and currently uses the CERQual instrument.

The quality of the qualitative studies identified is assessed by means of the following aspects, which are based on the Critical Appraisal Skills Programme (CASP) checklist [149]:

- Are the research question and/or the aims of the study described?
- Is the sampling strategy described?
- Is the sample described and suitable for the research question?
- Are the methods for data collection described and are they suitable for the topic?
- Are the methods for data analysis described?

- Were at least 2 researchers involved in the data analysis?
- Is the process of data analysis described transparently and comprehensibly?
- Are the study results presented clearly?

After extraction of the studies included, an overarching analysis and a descriptive summary of the results are performed. Furthermore, potential information needs are derived from the results.

9.4.2 Qualitative studies in the production of other IQWiG products

Different sources of information can support the production of systematic reviews [185,462,700]. One possible source are research results from qualitative studies [318,462,520,700]. Qualitative research can, among other things, provide information on the acceptance, suitability and implementation of interventions in clinical practice [30,184,460,518]. The results of qualitative research can be helpful in the interpretation of a systematic review [700] and may be used in the context of primary studies or systematic reviews in order to determine patient-relevant outcomes [184,186,441,519,520].

The Institute can use qualitative research findings to identify patient-relevant outcomes, and to present background information on patients' experiences and on the patient relevance of the intervention to be assessed. The Institute can also use these findings in the discussion and interpretation of results of a systematic review. In addition, in the HTA reports (see Sections 6.5.3 to 6.5.6), results from qualitative surveys and analyses (individual or focus group interviews) performed by external experts commissioned by IQWiG, as well as results from qualitative studies and reviews, form the basis for processing the domains of ethics and social and organizational issues.

Appendix A – Rationale of the methodological approach for determining the extent of added benefit

This appendix describes the rationale of the methodological approach for determining the extent of added benefit according to the Regulation for Early Benefit Assessment of New Pharmaceuticals (ANV[68]).

According to §5 (4) Sentence 1 of ANV, the dossier must present and consequently also assess "the extent to which there is added benefit". For this purpose, §5 (7) ANV contains a classification into 6 categories: (1) major added benefit, (2) considerable added benefit, (3) minor added benefit, (4) non-quantifiable added benefit, (5) no added benefit proven, (6) less benefit. For the Categories 1 to 3, §5 (7) ANV also provides a definition, as well as examples of criteria for particular consideration, as orientation for the presentation and assessment. These criteria describe qualitative characteristics (type of outcome) and also explicitly quantitative characteristics (e.g. major vs. moderate increase in survival time). In addition, a hierarchical ranking of outcomes is obviously intended, as sometimes the same modifier (e.g. relevant) results in a different extent of added benefit for different outcomes. The corresponding details of the primarily relevant extent categories of added benefit (minor, considerable, major) are shown in Table 11. On the basis of these requirements, it was IQWiG's responsibility to operationalize the extent of added benefit for the benefit assessment.

The criteria provided in §5 (7) ANV for the extent of added benefit designate (legal) terms. Some of these terms are clearly defined (e.g. survival time, serious adverse effects) and some are not (e.g. "alleviation of serious symptoms"). In addition, the criteria listed are not allocated to all categories. For instance, examples of survival time are given only for the categories considerable and major added benefit.

By using the wording "in particular" in §5 (7) with regard to the Categories 1 to 3, the legislator makes it clear that the criteria allocated to the categories are not to be regarded as conclusive. For instance, even if an increase in survival time is classified as less than moderate, it cannot be assumed that the legislator would not at least acknowledge a minor added benefit. Furthermore, the outcome "(health-related) quality of life", which is explicitly defined as a criterion of benefit in §2 (3) ANV, is not mentioned at all in the list of criteria for the extent of added benefit.

[68] Arzneimittel-Nutzenbewertungsverordnung, AM-NutzenV

Table 11: Determination of extent of added benefit – Criteria according to the ANV

Extent category	**Major** **sustained and great improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	Cure	Major increase in survival time	Long-term freedom from serious symptoms	Extensive avoidance of serious adverse effects
	Considerable **marked improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	Perceptible alleviation of the disease	Moderate increase in survival time	Alleviation of serious symptoms	Relevant avoidance of serious adverse effects Important avoidance of other adverse effects
	Minor **moderate and not only marginal improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy			Reduction in non-serious symptoms	Relevant avoidance of adverse effects
ANV: Arzneimittel-Nutzenbewertungsverordnung (Regulation for Early Benefit Assessment of New Pharmaceuticals)					

In a first step it is thus reasonable to extend the list of criteria by means of criteria that are qualitatively and quantitatively comparable. These amendments to the ANV requirements are shown in Table 12. In this context, the criteria "cure" and "perceptible alleviation of the disease" were not explicitly considered. The former generally requires operationalization. This should in principle be based on criteria referring to the outcomes "mortality" and "morbidity" (e.g. survival over a defined minimum period in patients with oncological diseases). As the ANV links "cure" solely to a major added benefit, the respective specific operationalization, on the basis of the outcomes used, must be examined with regard to whether this equals a relevant improvement in mortality or serious events. In this sense, a reduction in the duration of symptoms, for instance, in patients with simple infections, is not regarded as a "cure".

On the basis of the above amendments the outcome categories are restructured to illustrate the ranking of outcomes intended in the ANV and to consider disease severity according to §5 (7) ANV. For this purpose, the outcomes are grouped as follows, according to their relevance (see Table 13):

1. all-cause mortality
2. • serious (or severe) symptoms (or late complications)
   • serious or (severe) adverse effects
   • health-related quality of life
3. • non-serious (or non-severe) symptoms (or late complications)
   • non-serious (or non-severe) adverse effects

Health-related quality of life is regarded to be of equal importance as serious (or severe symptoms), late complications and adverse effects. The potential categories of extent of added benefit for non-serious outcomes are restricted to minor and considerable.

The requirements of the ANV make it clear that to determine the extent of added benefit, first the effect sizes must be described at outcome level. For each outcome separately the effect size – independent of its direction – is classified into 1 of the 3 extent categories (minor, considerable, major). Within the overall weighing of benefits and harms, these individual outcomes are then summarized into a global conclusion on the extent of added benefit. This step-by-step approach is described in Section 3.3.3.

Table 12: Determination of extent of added benefit – Criteria according to the ANV plus amendments[a]

		Outcome category			
		All-cause mortality	***Symptoms (morbidity)***	***Health-related quality of life***	***Adverse effects***
Extent category	**Major** **sustained and great improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	Major increase in survival time	*Long-term freedom from serious (or severe) symptoms (or late complications)*	*Major improvement in quality of life*	*Extensive avoidance of serious (or severe) adverse effects*
	Considerable **marked improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	Moderate increase in survival time	*Alleviation of serious (or severe) symptoms (or late complications)* *Important reduction in non-serious (or non-severe) symptoms (or late complications)*	*Important improvement in quality of life*	*Relevant avoidance of serious (or severe) adverse effects* *Important avoidance of other (non-serious or non-severe) adverse effects*
	Minor **moderate and not only marginal improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	*Any increase in survival time*	*Any reduction in serious (or severe) symptoms (or late complications)* *Reduction in non-serious (or non-severe) symptoms (or late complications)*	*Relevant improvement in quality of life*	*Any statistically significant reduction in serious (or severe) adverse effects* *Relevant avoidance of (other, non-serious or non-severe) adverse effects*

a. Amendments to the ANV in *italics*.

ANV: Arzneimittel-Nutzenbewertungsverordnung (Regulation for Early Benefit Assessment of New Pharmaceuticals)

Table 13: Determination of extent of added benefit – Ranked criteria according to the ANV plus amendments[a]

		Outcome category			
		All-cause mortality	**Serious *(or severe)* symptoms *(or late complications)* and adverse effects**	***Health-related quality of life***	**Non-serious *(or non-severe)* symptoms *(or late complications)* and adverse effects**
Extent category	**Major** **sustained and great improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	Major increase in survival time	Long-term freedom or extensive avoidance	*Major improvement*	*Not applicable*
	Considerable **marked improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	Moderate increase in survival time	Alleviation or relevant avoidance	*Important improvement*	Important avoidance
	Minor **moderate and not only marginal improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	*Any increase in survival time*	*Any reduction*	*Relevant improvement*	Relevant avoidance

a. Amendments to the ANV in *italics*.
ANV: Arzneimittel-Nutzenbewertungsverordnung (Regulation for Early Benefit Assessment of New Pharmaceuticals)

In accordance with §2 (3) ANV, the term benefit is defined as an effect and in §2 (4) ANV the term added benefit is defined as such an effect compared with the appropriate comparator therapy. It can be inferred from these definitions that the extent of added benefit must be determined by taking into account both the hierarchy of outcomes and effect sizes.

The ANV provides no details on the questions as to which effect sizes for the individual outcomes result in which extent category, or which effect measures should be chosen for the assessment. In principle, these questions can only be partly answered from a methodological point of view. Nevertheless, IQWiG is required to assess the extent of added benefit presented in the dossiers (§7 (2) ANV) and to draw its own conclusions on the extent. To restrict to a minimum at this stage the value judgements that will necessarily be made in the further deliberation process and to reveal them, the following measures are required:

- explicit operationalization to ensure a transparent approach
- abstract operationalization to achieve the best possible consistency between benefit assessments

Against this background a suitable effect measure must first be chosen. The initial focus is on the situation with binary data (analysis of 2x2 tables). In this context, relative effect measures – these mainly comprise the relative risk (RR) and the odds ratio (OR) – show the following advantages over absolute measures such as the risk difference (RD):

- The risk difference does not describe the effectiveness of therapy as such, as this difference strongly depends on the baseline risk in the control group. However, the baseline risk varies between regions, populations and over the course of time, as well as particularly between control groups receiving different comparator therapies. A risk difference should thus be interpreted as a descriptive measure of a specific study, not as a fixed measure of a specific treatment procedure; this is also and primarily a problem in meta-analyses [664]. This great susceptibility to external conditions calls into question the transferability of absolute effect measures from clinical studies to the daily health care setting. It is therefore common practice preferably to express effects shown in clinical studies as relative risks, odds ratios or hazard (or incidence) ratios [160].
- The degree of the risk difference is limited by the degree of the baseline risk (absolute risk in the control group). If this baseline risk is 1%, then the risk difference can never exceed 0.01 (or if it is 10%, the risk difference can never exceed 0.1 etc.). The risk difference could only reach the optimum value of 1 if the baseline risk was 100%. For instance, if an absolute risk reduction of at least 20% was defined as a substantial therapeutic improvement, then, for this example of a requirement, in diseases with (long-term) survival rates of greater than 80%, generally a major added benefit (for the corresponding outcome) would no longer be presentable.
- A further disadvantage of the use of the absolute risk reduction as an effect measure to operationalize the determination of the extent of added benefit is that an exact time point

must be defined at which this absolute risk reduction is determined (e.g. after 1, 2, 5 or 10 years), if no generally accepted definitions are available (e.g. 30-day mortality for myocardial infarction).

In summary, absolute risk reductions may have more of an impact in a situation of individual decision making, but relative effect measures are more suitable for general conclusions in terms of an assessment of the added benefit of a drug.

Relative measures have in common that the zero effect (no group difference) is 1. In the following text we address effects below 1, from which effects above 1 can be calculated by using the reciprocal. For the result to be classified as a minor, considerable or major added benefit, the approach stipulates that the (two-sided) 95% confidence interval of the effect undercuts the respective threshold in terms of a shift in the hypothesis boundary. In comparison with the examination of point estimates, such an inferential statistical approach has 2 main advantages: (i) The precision of the estimate is considered in the assessment; and accordingly, (ii) the probability of statistical errors can be limited to the usual small values (e.g. 5%).

The thresholds vary with regard to the 2 dimensions "outcome category" and "extent category (of the effect)" displayed in Table 13. The greater the relevance ascribed to the outcome, the closer the thresholds should lie to 1 (below 1). This takes into account the requirement from the ANV to consider disease severity. In contrast, the greater the determined extent of the effect, the further the thresholds should lie from 1 (below 1).

Following the explicit and abstract operationalization above, a division of the thresholds in step sizes of 0.05 is planned [379]. The further development of the methodological approach leading to these thresholds is briefly explained in the following text. The further deliberations will show that the choice of 0.05 is applicable in practice and leads to reasonable conclusions.

The starting point was formed by the question as to how large the actual effects have to be in order to be classified, for instance, as effects of a major extent. For this purpose, a relative risk of 0.50 – proposed by Djulbegovic et al. [188] as a requirement for a "breakthrough" – was defined as an effect of a major extent for the outcome "all-cause mortality" [379].

For this actual effect (0.5) the question arises as to how the threshold should be chosen to really achieve the extent "major" with adequate power. Details of the corresponding considerations can be found in the first dossier assessment conducted by the Institute [379], but are also addressed again at the end of this appendix. Following these considerations, the simultaneous requirements for feasibility and stringency can be regarded as fulfilled for a threshold of 0.85.

In a next step, for the matrix of the extent, the other actual effects are specified and the corresponding thresholds determined. In this context it should be considered that, on the basis of the outcome category "mortality", the requirements should increase for less serious outcomes, and on the basis of the extent category "major", should decrease for lower extent categories. In this context, a division into sixths for the actual effects was shown to be a

pragmatical solution. The thresholds for the respective extent categories are described in the following text.

1. All-cause mortality

With the usual significance level of 5%, any statistically significant increase in survival time is at least classified as minor added benefit, since for all-cause mortality the requirement that an effect should be "more than marginal" is regarded to be fulfilled by the outcome itself. The threshold referring to the 95% confidence interval is thus 1 here. An increase in survival time is classified as a considerable effect if a threshold of 0.95 is undercut. An increase in survival time is classified as being major if the threshold of 0.85 is undercut by the upper limit of the 95% confidence interval.

2.
- **Serious (or severe) symptoms (or late complications)**
- **serious or (severe) adverse effects**
- **health-related quality of life**

For serious (or severe) symptoms (or late complications) and serious (or severe) adverse effects, any statistically significant reduction also represents at least a minor effect, as the requirement of "more than marginal" is already fulfilled by the quality of the outcome itself. In contrast to the desired effects on all-cause mortality, a considerable effect requires that a threshold of 0.90 must be undercut and a "major" effect requires that a threshold of 0.75 is undercut. To derive a major effect from these outcomes also requires that the risk of the examined event should be at least 5% in at least one of the groups compared. This additional criterion supports the relevance of the event at population level and allows for the special requirements for this category of added benefit.

The precondition for determining the extent of added benefit for outcomes on health-related quality of life (as for all PROs) is that both the instruments applied and the response criteria must be validated or at least generally established. If these results are dichotomous in terms of responders and non-responders, the above criteria for serious symptoms apply (the risk for the category "major" should be at least 5%).

3.
- **Non-serious (or non-severe) symptoms (or late complications)**
- **non-serious (or non-severe) adverse effects**

The specification of thresholds for the non-serious (or non-severe) symptoms (or late complications) and the non-serious (or non-severe) adverse effects takes into account the lower severity compared with Categories 1 and 2.

As a matter of principle, the effect for non-serious outcomes should not be classified as major. To classify an effect as considerable or minor the thresholds of 0.80 or 0.90 respectively must be undercut. In the latter case, this is based on the requirement for minor added benefit specified in §5 (7) ANV that there must be a moderate, and not only marginal, improvement. The procedure thus implies that effects (also statistically significant ones) only assessed as marginal lead to classification into the category of no added benefit.

The corresponding thresholds for all extent categories and outcome categories are presented in the following Table 14.

Table 14: Inferential statistical thresholds (hypotheses boundaries) for relative effect measures

		Outcome category		
		All-cause mortality	Serious (or severe) symptoms (or late complications) and adverse effects, as well as quality of life[a]	Non-serious (or non-severe) symptoms (or late complications) and adverse effects
Extent category	Major	0.85	0.75 and risk ≥ 5%[b]	Not applicable
	Considerable	0.95	0.90	0.80
	Minor	1.00	1.00	0.90
a. Precondition (as for all patient-reported outcomes): use of a validated or established instrument, as well as a validated or established response criterion. b. Risk must be at least 5% for at least 1 of the 2 groups compared.				

Detailed methodological rationale for determination of thresholds

The starting point is the planning of a (fictional) study to test the conventional hypotheses

$H_0: RR \geq RR_0 \quad vs. \quad H_1: RR < RR_0$

on the basis of the relative risk $RR_0 = 1$. The required sample size is calculated by specifying the significance level, the power, the risk in the control group, and the actual effect (RR_1).

For all hypothesis boundaries shifted from 1 ($RR_0 < 1$) a study of this sort has reduced power. In order to maintain the same power for the shifted hypothesis boundary of interest (the thresholds named above) as specified for the testing of the conventional (non-shifted) hypotheses, the sample size must be increased – either within the study or through the combination of several studies. Assuming the normal case of 2 (e.g. pivotal) studies, it can be assumed that the sample size is twice as large.

The hypothesis boundary for the shifted hypotheses is then precisely selected so that the power for the conventional hypotheses of the 2 individual studies corresponds to the power for the shifted hypotheses of the combined (pooled) analysis. This hypothesis boundary serves as the threshold for the upper limit of the two-sided 95% confidence interval for the relative risk. For instance, the specification of a significance level of 5% (two-sided) and a power of 90% (both for the conventional and for the shifted hypothesis boundary), as well as a doubling of the sample size for the shifted hypothesis boundary resulted in a threshold of (rounded) 0.85 for the actual effect of 0.5 postulated for the outcome "mortality" and the extent category "major".

The formula included in Appendix A of the benefit assessment on ticagrelor [379] for the relationship between the actual effect and the threshold is independent of the other requirements and is based on the algorithm used in the "power" procedure of the software SAS. The

corresponding documentation for this algorithm [621] refers to the work by Fleiss et al. [248]. A query to Mr Röhmel (former Speaker of the Working Group "Pharmaceutical Research" of the German Region of the International Biometric Society), as well as directly to the Technical Support Section of SAS, showed that documentation of the validity of this algorithm has evidently not been published. The question arises as to which actual effects are required in more precise calculations to reach the respective extent category with high probability.

The actual effects were thus determined by means of Monte Carlo simulations as follows:

1) The significance level for the above hypothesis is 2.5% and the power is 90%. The parameter RR_1 runs through all values between 0.2 and 0.95 at a step size of 0.01. The risk in the control group p_C runs through all values between 0.05 and 0.95 at a step size of 0.05. For each of these tuples (RR_1, p_C) the required sample size n is calculated using $RR_0 = 1$ according to the formula by Farrington and Manning [235] and then doubled $(m \coloneqq 2n)$.
2) For each triple (RR_1, p_C, m) a threshold T runs through all values between 1 and 0 in a descending order with a step size of −0.005. For each T the power for the above hypothesis is approximated with $RR_0 = T$. The significance level is 2.5%. For this purpose 50 000 2x2 tables are simulated with a random generator, the upper confidence interval limit for the relative risk is calculated by means of the normal distribution approximation and the delta method for estimation of variance. Subsequently, the proportion of simulation cycles is determined for which the upper confidence interval limit is smaller than T. The T cycle is stopped as soon as an approximated power is smaller than 90%. The corresponding triple (RR_1, p_C, T) is documented in a list.
3) After the cycle of all parameters in Steps 1 and 2, all triples are chosen from the list for which the threshold T deviates less than 0.01 from one of the values 0.75, 0.80, 0.85, 0.90 and 0.95.

Figure 18 shows the resulting (more precise) actual effects, depending on the risk in the control group for all thresholds specified above (points approximated by smoothed curves).

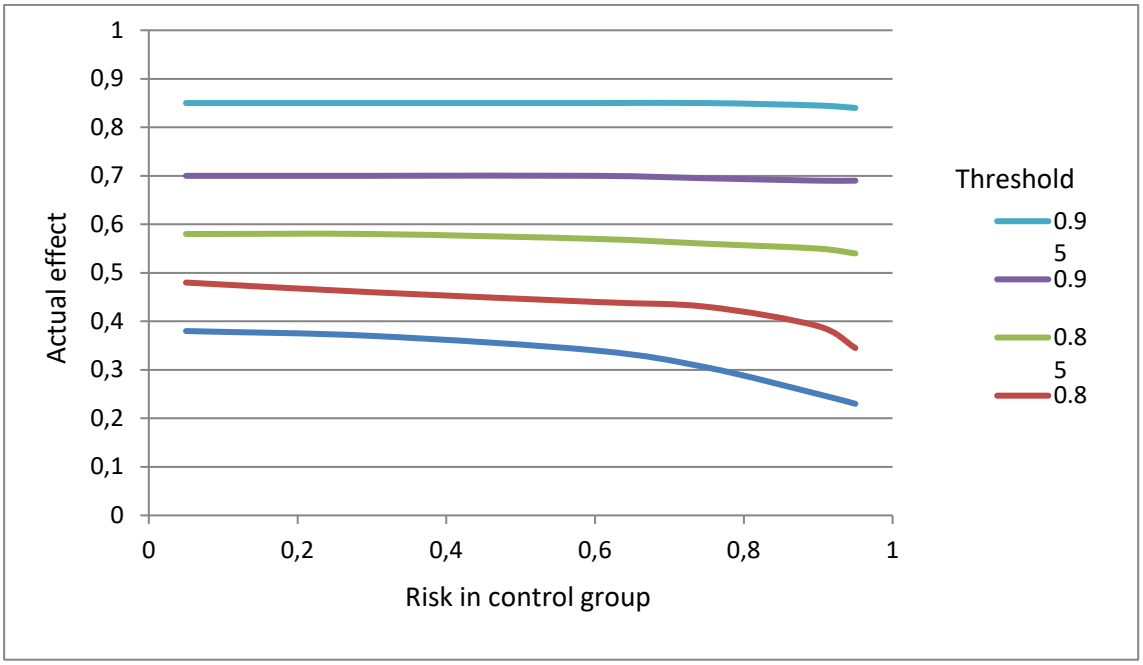


Figure 18: Actual effects depending on the baseline risk

Table 15 again contains the ranges (depending on the risk of the control group) in which the actual effects are realized, per outcome category and extent category.

Table 15: Actual effects for the relative risk

		Outcome category		
		All-cause mortality	Serious (or severe) symptoms (or late complications) and adverse effects as well as quality of life	Non-serious (or non-severe) symptoms (or late complications) and adverse effects
Extent category	Major	0.53–0.58	0.24–0.38	Not applicable
	Considerable	0.84–0.85	0.69–0.71	0.34–0.48
	Minor	Not applicable	Not applicable	0.69–0.71

In relation to all-cause mortality, actual relative risks of about 0.55 – i.e. still corresponding to about a halving of the risk – are to be specified for the extent "major". For the extent "considerable" the actual effect must lie at about 0.85. For serious symptoms and comparable outcomes, to be classified as a "major" extent, an actual reduction in risk to about a quarter to a third of the risk is required. Compared with the originally specified actual effects [379] good consistency is provided for thresholds lying close to 1. For the thresholds lying further away from 1, the simulation results show slightly more moderate requirements for the strength of the actual effects. The division of the thresholds as defined in Table 14 seems reasonable and practicable.

References

1. Memorandum for the evaluation of diagnostic measures. J Clin Chem Clin Biochem 1990; 28(12): 873-879.

2. Food and Drug Administration Amendments Act of 2007: Public Law 110–85 [online]. 2007 [Accessed: 01.02.2021]. URL: http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf.

3. Gesetz für eine bessere Versorgung durch Digitalisierung und Innovation (Digitale-Versorgung-Gesetz – DVG). Bundesgesetzblatt Teil 1 2019; (49): 2562-2584.

4. Sozialgesetzbuch (SGB) Fünftes Buch (V) - Gesetzliche Krankenversicherung - (Artikel 1 des Gesetzes v. 20. Dezember 1988, BGBl. I S. 2477) [online]. 2021 [Accessed: 05.08.2021]. URL: https://www.gesetze-im-internet.de/sgb_5/SGB_5.pdf.

5. Aagaard T, Lund H, Juhl C. Optimizing literature search in systematic reviews - are MEDLINE, EMBASE and CENTRAL enough for identifying effect studies within the area of musculoskeletal disorders? BMC Med Res Methodol 2016; 16(1): 161. https://dx.doi.org/10.1186/s12874-016-0264-6.

6. Ades AE, Caldwell DM, Reken S et al. Evidence synthesis for decision making 7: a reviewer's checklist. Med Decis Making 2013; 33(5): 679-691. https://dx.doi.org/10.1177/0272989X13485156.

7. Ades AE, Claxton K, Sculpher M. Evidence synthesis, parameter correlation and probabilistic sensitivity analysis. Health Econ 2006; 15(4): 373-381. https://dx.doi.org/10.1002/hec.1068.

8. AGREE Collaboration. Appraisal of guidelines for research & evaluation: AGREE instrument. London: St. George's Hospital Medical School; 2001.

9. AGREE Next Steps Consortium. Appraisal of Guidelines for REsearch & Evaluation II, AGREE II instrument [online]. 2017 [Accessed: 04.02.2021]. URL: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf.

10. Agresti A. Modelling ordered categorical data: recent advances and future challenges. Stat Med 1999; 18(17-18): 2191-2207. https://dx.doi.org/10.1002/(sici)1097-0258(19990915/30)18:17/18<2191::aid-sim249>3.0.co;2-m.

11. Agresti A. Categorical Data Analysis. Hoboken: Wiley; 2002.

12. Agresti A. Dealing with discreteness: making 'exact' confidence intervals for proportions, differences of proportions, and odds ratios more exact. Stat Methods Med Res 2003; 12(1): 3-21. https://dx.doi.org/10.1191/0962280203sm311ra.

13. Al-Marzouki S, Evans S, Marshall T et al. Are these data real? Statistical methods for the detection of data fabrication in clinical trials. BMJ 2005; 331(7511): 267-270. https://dx.doi.org/10.1136/bmj.331.7511.267.

14. Alma H, de Jong C, Jelusic D et al. Baseline health status and setting impacted minimal clinically important differences in COPD: an exploratory study. J Clin Epidemiol 2019; 116: 49-61. https://dx.doi.org/10.1016/j.jclinepi.2019.07.015.

15. Alma H, de Jong C, Tsiligianni I et al. Clinically relevant differences in COPD health status: systematic review and triangulation. Eur Respir J 2018; 52(3): 1800412. https://dx.doi.org/10.1183/13993003.00412-2018.

16. Altman DG. Systematic reviews of evaluations of prognostic variables. In: Egger M, Davey Smith G, Altman DG (Ed). Systematic reviews in health care: meta-analysis in context. London: BMJ Publishing Group; 2001. S. 228-247.

17. Altman DG, Bland JM. Absence of evidence is not evidence of absence. BMJ 1995; 311(7003): 485. https://dx.doi.org/10.1136/bmj.311.7003.485

18. Altman DG, Bland JM. Statistics notes. Units of analysis. BMJ 1997; 314(7098): 1874. https://dx.doi.org/10.1136/bmj.314.7098.1874.

19. Altman DG, Machin D, Bryant TN et al. Statistics with confidence; confidence intervals and statistical guidelines. London: BMJ Books; 2005.

20. Altman DG, McShane LM, Sauerbrei W et al. Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): explanation and elaboration. PLoS Med 2012; 9(5): e1001216. https://dx.doi.org/10.1371/journal.pmed.1001216.

21. American Society of Clinical Oncology. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. J Clin Oncol 1996; 14(2): 671-679. https://dx.doi.org/10.1200/JCO.1996.14.2.671.

22. Amir E, Seruga B, Martinez-Lopez J et al. Oncogenic targets, magnitude of benefit, and market pricing of antineoplastic drugs. J Clin Oncol 2011; 29(18): 2543-2549. https://dx.doi.org/10.1200/JCO.2011.35.2393.

23. Anthony L. AntConc; a freeware corpus analysis toolkit for concordancing and text analysis [online]. [Accessed: 04.02.2021]. URL: https://www.laurenceanthony.net/software/antconc/.

24. Antman EM, Lau J, Kupelnick B et al. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. JAMA 1992; 268(2): 240-248.

25. Arbeitsgruppe Erhebung und Nutzung von Sekundärdaten, Deutsche Gesellschaft für Sozialmedizin und Prävention, Deutsche Gesellschaft für Epidemiologie. Gute Praxis Sekundärdatenanalyse (GPS); Leitlinien und Empfehlungen [online]. 2014 [Accessed: 04.02.2021]. URL: https://www.dgepi.de/assets/Leitlinien-und-Empfehlungen/GPS_revision2-final_august2014.pdf.

26. Assasi N, Schwartz L, Tarride JE et al. Methodological guidance documents for evaluation of ethical considerations in health technology assessment: a systematic review. Expert Rev Pharmacoecon Outcomes Res 2014; 14(2): 203-220. https://dx.doi.org/10.1586/14737167.2014.894464.

27. Assmann SF, Pocock SJ, Enos LE et al. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000; 355(9209): 1064-1069. https://dx.doi.org/10.1016/S0140-6736(00)02039-0.

28. Atkins D, Best D, Briss PA et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328(7454): 1490. https://dx.doi.org/10.1136/bmj.328.7454.1490.

29. Atkins D, Eccles M, Flottorp S et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 2004; 4(1): 38. https://dx.doi.org/10.1186/1472-6963-4-38.

30. Atkins S, Lewin S, Smith H et al. Conducting a meta-ethnography of qualitative literature: lessons learnt. BMC Med Res Methodol 2008; 8: 21. https://dx.doi.org/10.1186/1471-2288-8-21.

31. Austin PC, Fine JP. Accounting for competing risks in randomized controlled trials: a review and recommendations for improvement. Stat Med 2017; 36(8): 1203-1209. https://dx.doi.org/10.1002/sim.7215.

32. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med 2017; 36(27): 4391-4400. https://dx.doi.org/10.1002/sim.7501.

33. Bafeta A, Trinquart L, Seror R et al. Reporting of results from network meta-analyses: methodological systematic review. BMJ 2014; 348: g1741. https://dx.doi.org/10.1136/bmj.g1741.

34. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature: Standards for use and reporting, with particular attention to one medical domain. J Clin Epidemiol 2001; 54(10): 979-985. https://dx.doi.org/10.1016/S0895-4356(01)00372-9.

35. Bai O, Chen M, Wang X. Bayesian Estimation and Testing in Random Effects Meta-analysis of Rare Binary Adverse Events. Stat Biopharm Res 2016; 8(1): 49-59. https://dx.doi.org/10.1080/19466315.2015.1096823.

36. Baio G. Bayesian Methods in Health Economics. Boca Raton: CRC Press; 2013.

37. Baker SG. Surrogate endpoints: wishful thinking or reality? J Natl Cancer Inst 2006; 98(8): 502-503. https://dx.doi.org/10.1093/jnci/djj153.

38. Balshem H, Stevens A, Ansari M et al. Finding Grey Literature Evidence and Assessing for Outcome and Analysis Reporting Biases When Comparing Medical Interventions: AHRQ and the Effective Health Care Program [online]. 2013 [Accessed: 04.02.2021]. URL: https://www.ncbi.nlm.nih.gov/books/NBK174882/pdf/Bookshelf_NBK174882.pdf.

39. Banta D. The development of health technology assessment. Health Policy 2003; 63(2): 121-132. https://dx.doi.org/10.1016/s0168-8510(02)00059-3.

40. Barro RJ, Sala-i-Martin X. World real interest rates [online]. 1990 [Accessed: 10.02.2021]. URL: https://www.nber.org/system/files/chapters/c10972/c10972.pdf.

41. Barron BA, Bukantz SC. The evaluation of new drugs. Current Food and drug Administration regulations and statistical aspects of clinical trials. Arch Intern Med 1967; 119(6): 547-556. https://dx.doi.org/10.1001/archinte.119.6.547.

42. Beauchamp TL. Methods and principles in biomedical ethics. J Med Ethics 2003; 29(5): 269-274. https://dx.doi.org/10.1136/jme.29.5.269.

43. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. New York: Oxford University Press; 2013.

44. Bell ML, Kenward MG, Fairclough DL et al. Differential dropout and bias in randomised controlled trials: when it matters and when it may not. BMJ 2013; 346: e8668. https://dx.doi.org/10.1136/bmj.e8668.

45. Bender R. Interpretation von Effizienzmaßen der Vierfeldertafel für Diagnostik und Behandlung. Med Klin (Munich) 2001; 96(2): 116-121. https://dx.doi.org/10.1007/pl00002179.

46. Bender R, Beckmann L. Limitations of the incidence density ratio as approximation of the hazard ratio. Trials 2019; 20(1): 485. https://dx.doi.org/10.1186/s13063-019-3590-2.

47. Bender R, Beckmann L, Lange S. Biometrical issues in the analysis of adverse events within the benefit assessment of drugs. Pharm Stat 2016; 15(4): 292-296. https://dx.doi.org/10.1002/pst.1740.

48. Bender R, Bunce C, Clarke M et al. Attention should be given to multiplicity issues in systematic reviews. J Clin Epidemiol 2008; 61(9): 857-865. https://dx.doi.org/10.1016/j.jclinepi.2008.03.004.

49. Bender R, Friede T, Koch A et al. Methods for evidence synthesis in the case of very few studies. Res Synth Methods 2018; 9(3): 382-392. https://dx.doi.org/10.1002/jrsm.1297.

50. Bender R, Grouven U. Logistic regression models used in medical research are poorly presented. BMJ 1996; 313: 628. https://dx.doi.org/10.1136/bmj.313.7057.628

51. Bender R, Grouven U. Ordinal logistic regression in medical research. J R Coll Physicians Lond 1997; 31(5): 546-551.

52. Bender R, Grouven U. Möglichkeiten und Grenzen statistischer Regressionsmodelle zur Berechnung von Schwellenwerten für Mindestmengen. Z Arztl Fortbild Qualitatssich 2006; 100(2): 93-98.

53. Bender R, Lange S. Adjusting for multiple testing—when and how? J Clin Epidemiol 2001; 54(4): 343-349. https://dx.doi.org/10.1016/s0895-4356(00)00314-0.

54. Bender R, Schwenke C, Schmoor C et al. Stellenwert von Ergebnissen aus indirekten Vergleichen: gemeinsame Stellungnahme von IQWiG, GMDS und IBS-DR [online]. 2012 [Accessed: 04.02.2021]. URL: https://www.iqwig.de/printprodukte/12-03-07_gemeinsame_stellungnahme_iqwig_gmds_ibs-dr_zum_indirekten_vergleich.pdf.

55. Bennett K, Duda S, Brouwers M et al. Towards high-quality, useful practice guidelines for child and youth mental health disorders: protocol for a systematic review and consensus exercise. BMJ Open 2018; 8(2): e018053. https://dx.doi.org/10.1136/bmjopen-2017-018053.

56. Bent S, Padula A, Avins AL. Brief communication: Better ways to question patients about adverse medical events: a randomized, controlled trial. Ann Intern Med 2006; 144(4): 257-261. https://dx.doi.org/10.7326/0003-4819-144-4-200602210-00007.

57. Beynon R, Leeflang MM, McDonald S et al. Search strategies to identify diagnostic accuracy studies in MEDLINE and EMBASE. Cochrane Database Syst Rev 2013; (9): MR000022. https://dx.doi.org/10.1002/14651858.MR000022.pub3.

58. Biesheuvel CJ, Grobbee DE, Moons KG. Distraction from randomization in diagnostic research. Ann Epidemiol 2006; 16(7): 540-544. https://dx.doi.org/10.1016/j.annepidem.2005.10.004.

59. Biglan A, Ary D, Wagenaar AC. The value of interrupted time-series experiments for community intervention research. Prev Sci 2000; 1(1): 31-49. https://dx.doi.org/10.1023/a:1010024016308.

60. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001; 69(3): 89-95. https://dx.doi.org/10.1067/mcp.2001.113989.

61. Bland JM, Altman DG. One and two sided tests of significance. BMJ 1994; 309(6949): 248. https://dx.doi.org/10.1136/bmj.309.6949.248.

62. Bock J, Toutenburg H. Sample size determination in clinical research. In: Rao CR, Chakraborty R (Ed). Statistical methods in biological and medical sciences. Amsterdam: Elsevier; 1991. S. 515-538.

63. Böhning D, Mylona K, Kimber A. Meta-analysis of clinical trials with rare events. Biom J 2015; 57(4): 633-648. https://dx.doi.org/10.1002/bimj.201400184.

64. Bonell C, Oakley A, Hargreaves J et al. Assessment of generalisability in trials of health interventions: suggested framework and systematic review. BMJ 2006; 333(7563): 346-349. https://dx.doi.org/10.1136/bmj.333.7563.346.

65. Bonhoeffer J, Zumbrunn B, Heininger U. Reporting of vaccine safety data in publications: systematic review. Pharmacoepidemiol Drug Saf 2005; 14(2): 101-106. https://dx.doi.org/10.1002/pds.979.

66. Borah R, Brown AW, Capers PL et al. Analysis of the time and workers needed to conduct systematic reviews of medical interventions using data from the PROSPERO registry. BMJ Open 2017; 7(2): e012545. https://dx.doi.org/10.1136/bmjopen-2016-012545.

67. Borm GF, Donders AR. Updating meta-analyses leads to larger type I errors than publication bias. J Clin Epidemiol 2009; 62(8): 825-830.e10. https://dx.doi.org/10.1016/j.jclinepi.2008.08.010.

68. Bossuyt PM, Irwig L, Craig J et al. Comparative accuracy: assessing new tests against existing diagnostic pathways. BMJ 2006; 332(7549): 1089-1092. https://dx.doi.org/10.1136/bmj.332.7549.1089.

69. Bossuyt PM, Lijmer JG, Mol BW. Randomised comparisons of medical tests: sometimes invalid, not always efficient. Lancet 2000; 356(9244): 1844-1847. https://dx.doi.org/10.1016/S0140-6736(00)03246-3.

70. Bossuyt PM, Reitsma JB, Bruns DE et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015; 351: h5527. https://dx.doi.org/10.1136/bmj.h5527.

71. Bossuyt PM, Reitsma JB, Bruns DE et al. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. Ann Intern Med 2003; 138(1): 40-44. https://dx.doi.org/10.7326/0003-4819-138-1-200301070-00010.

72. Bossuyt PM, Reitsma JB, Bruns DE et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Ann Intern Med 2003; 138(1): W1-12. https://dx.doi.org/10.7326/0003-4819-138-1-200301070-00012-w1.

73. Boutron I, Moher D, Altman DG et al. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med 2008; 148(4): 295-309. https://dx.doi.org/10.7326/0003-4819-148-4-200802190-00008.

74. Boutron I, Moher D, Altman DG et al. Methods and processes of the CONSORT Group: example of an extension for trials assessing nonpharmacologic treatments. Ann Intern Med 2008; 148(4): W60-66. https://dx.doi.org/10.7326/0003-4819-148-4-200802190-00008-w1.

75. Boutron I, Page MJ, Higgins JPT et al. Considering bias and conflicts of interest among the included studies. In: Higgins JPT, Thomas J, Chandler J et al (Ed). Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley-Blackwell; 2019. S. 177-204.

76. Bradburn MJ, Deeks JJ, Berlin JA et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2007; 26(1): 53-77. https://dx.doi.org/10.1002/sim.2528.

77. Brazier J, Roberts J, Tsuchiya A et al. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ 2004; 13(9): 873-884. https://dx.doi.org/10.1002/hec.866.

78. Breslow NE, Day NE. Statistical Methods in Cancer Research; Volume 1 - The analysis of case-control studies [online]. 1980 [Accessed: 17.02.2021]. URL: https://publications.iarc.fr/_publications/media/download/3468/200a06ebe55fa3d17ed551c5fcdb83f5cf0f3752.pdf.

79. Breslow NE, Day NE. Statistical Methods in Cancer Research; Volume II - The Design and Analysis of Cohort Studies [online]. 1987 [Accessed: 17.02.2021]. URL: https://publications.iarc.fr/_publications/media/download/3494/fb469ed43c52f0c738915cca6a0f31544b9ed7b6.pdf.

80. Bridges JF, Hauber AB, Marshall D et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health 2011; 14(4): 403-413. https://dx.doi.org/10.1016/j.jval.2010.11.013.

81. Bridges JF, Kinter ET, Kidane L et al. Things are Looking up Since We Started Listening to Patients: Trends in the Application of Conjoint Analysis in Health 1982-2007. Patient 2008; 1(4): 273-282. https://dx.doi.org/10.2165/01312067-200801040-00009.

82. Briggs AH, Weinstein MC, Fenwick EA et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. Med Decis Making 2012; 32(5): 722-732. https://dx.doi.org/10.1177/0272989X12458348.

83. Brockhaus AC, Bender R, Skipka G. The Peto odds ratio viewed as a new effect measure. Stat Med 2014; 33(28): 4861-4874. https://dx.doi.org/10.1002/sim.6301.

84. Brockhaus AC, Grouven U, Bender R. Performance of the Peto odds ratio compared to the usual odds ratio estimator in the case of rare events. Biom J 2016; 58(6): 1428-1444. https://dx.doi.org/10.1002/bimj.201600034.

85. Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. Stat Med 2001; 20(6): 825-840. https://dx.doi.org/10.1002/sim.650.

86. Brok J, Thorlund K, Gluud C et al. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol 2008; 61(8): 763-769. https://dx.doi.org/10.1016/j.jclinepi.2007.10.007.

87. Brok J, Thorlund K, Wetterslev J et al. Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol 2009; 38(1): 287-298. https://dx.doi.org/10.1093/ije/dyn188.

88. Brookes ST, Whitely E, Egger M et al. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol 2004; 57(3): 229-236. https://dx.doi.org/10.1016/j.jclinepi.2003.08.009.

89. Brouwer W, Rutten F, Koopmanschap M. Costing in economic evaluations. In: Drummond M, McGuire A (Ed). Economic evaluation in health care: merging theory with practice. Oxford: Oxford University Press; 2001. S. 68-93.

90. Brouwer WB, Culyer AJ, van Exel NJ et al. Welfarism vs. extra-welfarism. J Health Econ 2008; 27(2): 325-338. https://dx.doi.org/10.1016/j.jhealeco.2007.07.003.

91. Brouwer WB, Koopmanschap MA, Rutten FF. Productivity costs in cost-effectiveness analysis: numerator or denominator: a further discussion. Health Econ 1997; 6(5): 511-514. https://dx.doi.org/10.1002/(sici)1099-1050(199709)6:5<511::aid-hec297>3.0.co;2-k.

92. Brouwer WB, Koopmanschap MA, Rutten FF. Productivity costs measurement through quality of life? A response to the recommendation of the Washington Panel. Health Econ 1997; 6(3): 253-259. https://dx.doi.org/10.1002/(sici)1099-1050(199705)6:3<253::aid-hec266>3.0.co;2-6.

93. Brouwers MC, Kho ME, Browman GP et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 2010; 182(18): E839-842. https://dx.doi.org/10.1503/cmaj.090449.

94. Brouwers MC, Kho ME, Browman GP et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. CMAJ 2010; 182(10): 1045-1052. https://dx.doi.org/10.1503/cmaj.091714.

95. Brouwers MC, Kho ME, Browman GP et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. CMAJ 2010; 182(10): E472-478. https://dx.doi.org/10.1503/cmaj.091716.

96. Brown H, Prescott R. Applied Mixed Models in Medicine. Chichester: Wiley; 2006.

97. Brozek JL, Akl EA, Alonso-Coello P et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy 2009; 64(5): 669-677. https://dx.doi.org/10.1111/j.1398-9995.2009.01973.x.

98. Brozek JL, Akl EA, Compalati E et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. Allergy 2011; 66(5): 588-595. https://dx.doi.org/10.1111/j.1398-9995.2010.02530.x.

99. Brozek JL, Akl EA, Jaeschke R et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines: Part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. Allergy 2009; 64(8): 1109-1116. https://dx.doi.org/10.1111/j.1398-9995.2009.02083.x.

100. Brundage M, Blazeby J, Revicki D et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. Qual Life Res 2013; 22(6): 1161-1175. https://dx.doi.org/10.1007/s11136-012-0252-1.

101. Bucher HC, Guyatt GH, Griffith LE et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50(6): 683-691. https://dx.doi.org/10.1016/s0895-4356(97)00049-8.

102. Büchter RB, Fechtelpeter D, Knelangen M et al. Words or numbers? Communicating risk of adverse effects in written consumer health information: a systematic review and meta-analysis. BMC Med Inform Decis Mak 2014; 14: 76. https://dx.doi.org/10.1186/1472-6947-14-76.

103. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Programm für Nationale VersorgungsLeitlinien; Methodenreport [online]. 2017 [Accessed: 05.08.2021]. URL: https://www.leitlinien.de/methodik/pdf/nvl-methodenreport-5aufl-vers1.pdf.

104. Bundesinstitut für Arzneimittel und Medizinprodukte. PharmNet.Bund-Arzneimittel-Informationssystem [online]. 2020 [Accessed: 04.02.2021]. URL: https://www.pharmnet-bund.de/dynamic/de/arzneimittel-informationssystem/index.html.

105. Bundesministerium der Justiz. Verordnung zur Schaffung barrierefreier Informationstechnik nach dem Behindertengleichstellungsgesetz (Barrierefreie-Informationstechnik-Verordnung - BITV 2.0) [online]. 2019 [Accessed: 04.02.2021]. URL: http://www.gesetze-im-internet.de/bitv_2_0/BJNR184300011.html.

106. Bundesministerium für Gesundheit. Verordnung über die Nutzenbewertung von Arzneimitteln nach § 35a Absatz 1 SGB V für Erstattungsvereinbarungen nach § 130b SGB V (Arzneimittel-Nutzenbewertungsverordnung - AM-NutzenV) [online]. 2019 [Accessed: 04.02.2021]. URL: http://www.gesetze-im-internet.de/am-nutzenv/AM-NutzenV.pdf.

107. Bundesministerium für Gesundheit. Verordnung über die Verfahrensgrundsätze der Bewertung von Untersuchungs- und Behandlungsmethoden in der vertragsärztlichen Versorgung und im Krankenhaus (Methodenbewertungsverfahrensverordnung - MBVerfV) [online]. 2020 [Accessed: 04.02.2021]. URL: http://www.gesetze-im-internet.de/mbverfv/MBVerfV.pdf.

108. Bundesministerium für Gesundheit, Bundesministerium für Bildung und Forschung. Verordnung über die Voraussetzungen für die Bewertung neuer Untersuchungs- und Behandlungsmethoden mit Medizinprodukten hoher Risikoklasse nach § 137h des Fünften Buches Sozialgesetzbuch (Medizinproduktemethodenbewertungsverordnung - MeMBV) [online]. 2021 [Accessed: 29.06.2021]. URL: http://www.gesetze-im-internet.de/membv/MeMBV.pdf.

109. Bundessozialgericht. Urteil - 06.05.2009 - B 6 A 1/08 R [online]. 2009 [Accessed: 04.02.2021]. URL: https://sozialgerichtsbarkeit.de/sgb/esgb/export.php?modul=esgb&id=121138&exportformat=PDF.

110. Bundesverfassungsgericht. Leitsatz zum Beschluss des Ersten Senats vom 6. Dezember 2005 - 1 BvR 347/98 - [online]. 2005 [Accessed: 05.08.2021]. URL: https://www.bundesverfassungsgericht.de/SharedDocs/Downloads/DE/2005/12/rs20051206_1bvr034798.pdf?__blob=publicationFile&v=1.

111. Burton P, Gurrin L, Sly P. Extending the simple linear regression model to account for correlated responses: an introduction to generalized estimating equations and multi-level mixed modelling. Stat Med 1998; 17(11): 1261-1291. https://dx.doi.org/10.1002/(sici)1097-0258(19980615)17:11<1261::aid-sim846>3.0.co;2-z.

112. Burzykowski T, Buyse M. Surrogate threshold effect: an alternative measure for meta-analytic surrogate endpoint validation. Pharm Stat 2006; 5(3): 173-186. https://dx.doi.org/10.1002/pst.207.

113. Burzykowski T, Molenberghs G, Buyse M. The Evaluation of Surrogate Endpoints. New York: Springer; 2005.

114. Buxton MJ, Drummond MF, Van Hout BA et al. Modelling in economic evaluation: an unavoidable fact of life. Health Econ 1997; 6(3): 217-227. https://dx.doi.org/10.1002/(sici)1099-1050(199705)6:3<217::aid-hec267>3.0.co;2-w.

115. Buyse M, Molenberghs G, Burzykowski T et al. The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics 2000; 1(1): 49-67. https://dx.doi.org/10.1093/biostatistics/1.1.49.

116. Cairns J. Discounting in economic evaluation. In: Drummond MF, McGuire A (Ed). Economic evaluation in health care; merging theory with practice. Oxford: Oxford University Press; 2001. S. 236-255.

117. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005; 331(7521): 897-900. https://dx.doi.org/10.1136/bmj.331.7521.897.

118. Calvert M, Blazeby J, Altman DG et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. JAMA 2013; 309(8): 814-822. https://dx.doi.org/10.1001/jama.2013.879.

119. Campbell MK, Piaggio G, Elbourne DR et al. Consort 2010 statement: extension to cluster randomised trials. BMJ 2012; 345: e5661. https://dx.doi.org/10.1136/bmj.e5661.

120. Canadian Agency for Drugs and Technologies in Health. Guidelines for the Economic Evaluation of Health Technologies: Canada; CADTH Methods and Guidelines [online]. 2017 [Accessed: 04.02.2021]. URL: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

121. Canestaro WJ, Hendrix N, Bansal A et al. Favorable and publicly funded studies are more likely to be published: a systematic review and meta-analysis. J Clin Epidemiol 2017; 92: 58-68. https://dx.doi.org/10.1016/j.jclinepi.2017.08.004.

122. Caro JJ, Ishak KJ. No head-to-head trial? simulate the missing arms. Pharmacoeconomics 2010; 28(10): 957-967. https://dx.doi.org/10.2165/11537420-000000000-00000.

123. Carrasco-Labra A, Devji T, Qasim A et al. Interpretation of patient-reported outcome measures: an inventory of over 3000 minimally important difference estimates and an assessment of their credibility. Cochrane Database Syst Rev 2018; (9 Suppl 1): 135-136. https://dx.doi.org/10.1002/14651858.CD201801.

124. Carroll RJ, Ruppert D, Stefanski LA et al. Measurement error in nonlinear models; a modern perspective. London: Chapman & Hall; 2006.

125. Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. BMJ 2015; 350: g7773. https://dx.doi.org/10.1136/bmj.g7773.

126. Carter SM, Rogers W, Heath I et al. The challenge of overdiagnosis begins with its definition. BMJ 2015; 350: h869. https://dx.doi.org/10.1136/bmj.h869.

127. Celik D, Coban Ö, Kilicoglu Ö. Minimal clinically important difference of commonly used hip-, knee-, foot-, and ankle-specific questionnaires: a systematic review. J Clin Epidemiol 2019; 113: 44-57. https://dx.doi.org/10.1016/j.jclinepi.2019.04.017.

128. Centre for Reviews and Dissemination. PROSPERO; International prospective register of systematic reviews [online]. [Accessed: 04.02.2021]. URL: https://www.crd.york.ac.uk/PROSPERO/.

129. Centre for Reviews and Dissemination. Systematic reviews; CRD's guidance for undertaking reviews in health care [online]. 2009 [Accessed: 09.02.2021]. URL: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.

130. Chan AW, Hrobjartsson A, Haahr MT et al. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA 2004; 291(20): 2457-2465. https://dx.doi.org/10.1001/jama.291.20.2457.

131. Chavalarias D, Ioannidis JP. Science mapping analysis characterizes 235 biases in biomedical research. J Clin Epidemiol 2010; 63(11): 1205-1215. https://dx.doi.org/10.1016/j.jclinepi.2009.12.011.

132. Cheng CL, Van Ness JW. Statistical regression with measurement error. London: Arnold; 1999.

133. Chi C. Shall we search all trial registers? A comparative study of the sensitivity of five trial registers used by the Cochrane Skin Group [online]. 2012 [Accessed: 04.02.2021]. URL: https://abstracts.cochrane.org/2012-auckland/shall-we-search-all-trial-registers-comparative-study-sensitivity-five-trial-registers.

134. Chiou CF, Hay JW, Wallace JF et al. Development and validation of a grading system for the quality of cost-effectiveness studies. Med Care 2003; 41(1): 32-44. https://dx.doi.org/10.1097/00005650-200301000-00007.

135. Ciani O, Buyse M, Garside R et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. BMJ 2013; 346: f457. https://dx.doi.org/10.1136/bmj.f457.

136. Clarivate Analytics. EndNote [online]. [Accessed: 04.02.2021]. URL: https://endnote.com/.

137. Clark MD, Determann D, Petrou S et al. Discrete choice experiments in health economics: a review of the literature. Pharmacoeconomics 2014; 32(9): 883-902. https://dx.doi.org/10.1007/s40273-014-0170-x.

138. Claxton K, Paulden M, Gravelle H et al. Discounting and decision making in the economic evaluation of health-care technologies. Health Econ 2011; 20(1): 2-15. https://dx.doi.org/10.1002/hec.1612.

139. Cochrane Effective Practice and Organisation of Care Review Group. Data collection checklist [online]. 2002 [Accessed: 04.02.2021]. URL: http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/datacollectionchecklist.pdf.

140. Collins GS, Reitsma JB, Altman DG et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015; 350: g7594. https://dx.doi.org/10.1136/bmj.g7594.

141. Commission of the European Communities. eEurope 2002: Quality Criteria for Health related Websites [online]. 2002 [Accessed: 04.02.2021]. URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2002:0667:FIN:EN:PDF.

142. Committee of Experts on Management of Safety and Quality in Health Care, Expert Group on Safe Medication Practices. Glossary of terms related to patient and medication safety [online]. 2005 [Accessed: 04.02.2021]. URL: http://www.who.int/patientsafety/highlights/COE_patient_and_medication_safety_gl.pdf.

143. Concannon TW, Fuster M, Saunders T et al. A systematic review of stakeholder engagement in comparative effectiveness and patient-centered outcomes research. J Gen Intern Med 2014; 29(12): 1692-1701. https://dx.doi.org/10.1007/s11606-014-2878-x.

144. Cooper C, Booth A, Britten N et al. A comparison of results of empirical studies of supplementary search techniques and recommendations in review methodology handbooks: a methodological review. Syst Rev 2017; 6(1): 234. https://dx.doi.org/10.1186/s13643-017-0625-1.

145. Corbin JM, Strauss AL. Weiterleben lernen; Verlauf und Bewältigung chronischer Krankheiten. Bern: Huber; 2010.

146. Cordoba G, Schwartz L, Woloshin S et al. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. BMJ 2010; 341: c3920. https://dx.doi.org/10.1136/bmj.c3920.

147. Cornell JE, Laine C. The science and art of deduction: complex systematic overviews. Ann Intern Med 2008; 148(10): 786-788. https://dx.doi.org/10.7326/0003-4819-148-10-200805200-00012.

148. Craig P, Dieppe P, Macintyre S et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008; 337: a1655. https://dx.doi.org/10.1136/bmj.a1655.

149. Critical Appraisal Skills Programme. CASP Checklist: 10 questions to help you make sense of a Qualitative research [online]. 2018 [Accessed: 10.08.2021]. URL: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Qualitative-Checklist-2018_fillable_form.pdf.

150. Cui L, Hung HM, Wang SJ et al. Issues related to subgroup analysis in clinical trials. J Biopharm Stat 2002; 12(3): 347-358. https://dx.doi.org/10.1081/bip-120014565.

151. D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues - the encounters of academic consultants in statistics. Stat Med 2003; 22(2): 169-186. https://dx.doi.org/10.1002/sim.1425.

152. da Costa BR, Rutjes AW, Johnston BC et al. Methods to convert continuous outcomes into odds ratios of treatment response and numbers needed to treat: meta-epidemiological study. Int J Epidemiol 2012; 41(5): 1445-1459. https://dx.doi.org/10.1093/ije/dys124.

153. Daly J, Willis K, Small R et al. A hierarchy of evidence for assessing qualitative health research. J Clin Epidemiol 2007; 60(1): 43-49. https://dx.doi.org/10.1016/j.jclinepi.2006.03.014.

154. Damarell RA, Tieman JJ, Sladek RM. OvidSP Medline-to-PubMed search filter translation: a methodology for extending search filter range to include PubMed's unique content. BMC Med Res Methodol 2013; 13: 86. https://dx.doi.org/10.1186/1471-2288-13-86.

155. Danner M, Hummel JM, Volz F et al. Integrating patients' views into health technology assessment: Analytic hierarchy process (AHP) as a method to elicit patient preferences. Int J Technol Assess Health Care 2011; 27(4): 369-375. https://dx.doi.org/10.1017/S0266462311000523.

156. Dans AL, Dans LF, Guyatt GH et al. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. JAMA 1998; 279(7): 545-549. https://dx.doi.org/10.1001/jama.279.7.545.

157. Dans LF, Silvestre MA, Dans AL. Trade-off between benefit and harm is crucial in health screening recommendations. Part I: general principles. J Clin Epidemiol 2011; 64(3): 231-239. https://dx.doi.org/10.1016/j.jclinepi.2010.09.009.

158. De Angelis CD, Drazen JM, Frizelle FA et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. Ann Intern Med 2005; 143(2): 146-148. https://dx.doi.org/10.7326/0003-4819-143-2-200507190-00016.

159. Deeks JJ. Systematic reviews in health care: Systematic reviews of evaluations of diagnostic and screening tests. BMJ 2001; 323(7305): 157-162. https://dx.doi.org/10.1136/bmj.323.7305.157.

160. Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. Stat Med 2002; 21(11): 1575-1600. https://dx.doi.org/10.1002/sim.1188.

161. Deeks JJ, Higgins JPT, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J et al (Ed). Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley-Blackwell; 2019. S. 241-284.

162. Derksen S, Keselman HJ. Backward, forward, and stepwise automated subset selection algorithms: frequency of obtaining authentic and noise variables. Br J Math Stat Psychol 1992; 45(2): 265-282. https://dx.doi.org/10.1111/j.2044-8317.1992.tb00992.x.

163. Derry S, Loke YK, Aronson JK. Incomplete evidence: the inadequacy of databases in tracing published adverse drug reactions in clinical trials. BMC Med Res Methodol 2001; 1: 7. https://dx.doi.org/10.1186/1471-2288-1-7.

164. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3): 177-188. https://dx.doi.org/10.1016/0197-2456(86)90046-2.

165. Des Jarlais DC, Lyles C, Crepaz N et al. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. Am J Public Health 2004; 94(3): 361-366. https://dx.doi.org/10.2105/ajph.94.3.361.

166. Desroches B, Francis M. World Real Interest Rates: A Global Savings and Investment Perspective [online]. 2007 [Accessed: 04.02.2021]. URL: http://www.bankofcanada.ca/wp-content/uploads/2010/03/wp07-16.pdf.

167. Desu MM, Raghavarao D. Sample size methodology. Boston: Academic Press; 1990.

168. Deutsche Gesellschaft für Epidemiologie. Leitlinien und Empfehlungen zur Sicherung von Guter Epidemiologischer Praxis (GEP); Langversion [online]. 2018 [Accessed: 04.02.2021]. URL: https://www.dgepi.de/assets/Leitlinien-und-Empfehlungen/Leitlinien_fuer_Gute_Epidemiologische_Praxis_GEP_vom_September_2018.pdf.

169. Deutscher Bundestag. Gesetz zur Modernisierung der gesetzlichen Krankenversicherung (GKV-Modernisierungsgesetz - GMG). Bundesgesetzblatt Teil 1 2003; (55): 2190-2258.

170. Deutscher Bundestag. Gesetzentwurf der Fraktionen SPD, CDU/CSU und BÜNDNIS 90/DIE GRÜNEN: Entwurf eines Gesetzes zur Modernisierung der gesetzlichen Krankenversicherung (GKV-Modernisierungsgesetz - GMG) [online]. 2003 [Accessed: 04.02.2021]. URL: http://dipbt.bundestag.de/doc/btd/15/015/1501525.pdf.

171. Deutscher Bundestag. Gesetz zur Neuordnung des Arzneimittelmarktes in der gesetzlichen Krankenversicherung (Arzneimittelmarktneuordnungsgesetz – AMNOG) vom 22. Dezember 2010. Bundesgesetzblatt Teil 1 2010; (67): 2262-2277.

172. Deutscher Ethikrat. Nutzen und Kosten im Gesundheitswesen – Zur normativen Funktion ihrer Bewertung; Stellungnahme [online]. 2011 [Accessed: 05.02.2021]. URL: https://www.ethikrat.org/fileadmin/Publikationen/Stellungnahmen/deutsch/DER_StnAllo-Aufl2_Online.pdf.

173. Deutsches Institut für Normung. Klinische Prüfung von Medizinprodukten an Menschen; gute klinische Praxis (ISO 14155:2011 + Cor. 1:2011); deutsche Fassung EN ISO 14155:2011 + AC:2011. Berlin: Beuth; 2012.

174. Deutsches Netzwerk Evidenzbasierte Medizin. Die ‚Gute Praxis Gesundheitsinformation'. Z Evid Fortbild Qual Gesundhwes 2010; 104(1): 66-68. https://dx.doi.org/10.1016/j.zefq.2009.12.018.

175. Deutsches Netzwerk Evidenzbasierte Medizin. Gute Praxis Gesundheitsinformation: ein Positionspapier des Deutschen Netzwerks Evidenzbasierte Medizin e.V. [online]. 2016 [Accessed: 21.11.2019]. URL: https://www.ebm-netzwerk.de/de/medien/pdf/gpgi_2_20160721.pdf.

176. Deville WL, Buntinx F, Bouter LM et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. BMC Med Res Methodol 2002; 2: 9. https://dx.doi.org/10.1186/1471-2288-2-9.

177. Devji T, Carrasco-Labra A, Lytvyn L et al. A new tool to measure credibility of studies determining minimally important difference estimates. Cochrane Database Syst Rev 2017; (9 Suppl 1): 58. https://dx.doi.org/10.1002/14651858.CD201702.

178. Devji T, Carrasco-Labra A, Qasim A et al. Evaluating the credibility of anchor based estimates of minimal important differences for patient reported outcomes: instrument development and reliability study. BMJ 2020; 369: m1714. https://dx.doi.org/10.1136/bmj.m1714.

179. Devji T, Guyatt GH, Lytvyn L et al. Application of minimal important differences in degenerative knee disease outcomes: a systematic review and case study to inform BMJ Rapid Recommendations. BMJ Open 2017; 7(5): e015587. https://dx.doi.org/10.1136/bmjopen-2016-015587.

180. Di Pietrantonj C. Four-fold table cell frequencies imputation in meta analysis. Stat Med 2006; 25(13): 2299-2322. https://dx.doi.org/10.1002/sim.2287.

181. Dias S, Welton NJ, Caldwell DM et al. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010; 29(7-8): 932-944. https://dx.doi.org/10.1002/sim.3767.

182. DIPEx. Healthtalk.org [online]. [Accessed: 04.02.2021]. URL: http://www.healthtalk.org/.

183. Dixon-Woods M. Writing wrongs? An analysis of published discourses about the use of patient information leaflets. Soc Sci Med 2001; 52(9): 1417-1432. https://dx.doi.org/10.1016/s0277-9536(00)00247-1.

184. Dixon-Woods M, Agarwal S, Young B et al. Integrative approaches to qualitative and quantitative evidence [online]. 2004 [Accessed: 05.02.2021]. URL: https://www.webarchive.org.uk/wayback/archive/20140616160402mp_/http://nice.org.uk/nicemedia/documents/integrative_approaches.pdf.

185. Dixon-Woods M, Fitzpatrick R. Qualitative research in systematic reviews. Has established a place for itself. BMJ 2001; 323(7316): 765-766. https://dx.doi.org/10.1136/bmj.323.7316.765.

186. Dixon-Woods M, Fitzpatrick R, Roberts K. Including qualitative research in systematic reviews: opportunities and problems. J Eval Clin Pract 2001; 7(2): 125-133. https://dx.doi.org/10.1046/j.1365-2753.2001.00257.x.

187. Dixon-Woods M, Sutton A, Shaw R et al. Appraising qualitative research for inclusion in systematic reviews: a quantitative and qualitative comparison of three methods. J Health Serv Res Policy 2007; 12(1): 42-47. https://dx.doi.org/10.1258/135581907779497486.

188. Djulbegovic B, Kumar A, Soares HP et al. Treatment success in cancer: new cancer treatment successes identified in phase 3 randomized controlled trials conducted by the National Cancer Institute-sponsored cooperative oncology groups, 1955 to 2006. Arch Intern Med 2008; 168(6): 632-642. https://dx.doi.org/10.1001/archinte.168.6.632.

189. Doganay Erdogan B, Leung YY, Pohl C et al. Minimal Clinically Important Difference as Applied in Rheumatology: An OMERACT Rasch Working Group Systematic Review and Critique. J Rheumatol 2016; 43(1): 194-202. https://dx.doi.org/10.3899/jrheum.141150.

190. Dolan JG. Shared decision-making--transferring research into practice: the Analytic Hierarchy Process (AHP). Patient Educ Couns 2008; 73(3): 418-425. https://dx.doi.org/10.1016/j.pec.2008.07.032.

191. Dolan JG, Isselhardt BJ Jr, Cappuccio JD. The analytic hierarchy process in medical decision making: a tutorial. Med Decis Making 1989; 9(1): 40-50. https://dx.doi.org/10.1177/0272989X8900900108.

192. Dolan P, Edlin R, Tsuchiya A. The relative societal value of health gains to different beneficiaries [online]. 2008 [Accessed: 05.08.2021]. URL: http://eprints.whiterose.ac.uk/10902/1/HEDS_DP_08-12.pdf.

193. Dolan P, Shaw R, Tsuchiya A et al. QALY maximisation and people's preferences: a methodological review of the literature. Health Econ 2005; 14(2): 197-208. https://dx.doi.org/10.1002/hec.924.

194. Donegan S, Williamson P, D'Alessandro U et al. Assessing key assumptions of network meta-analysis: a review of methods. Res Synth Methods 2013; 4(4): 291-323. https://dx.doi.org/10.1002/jrsm.1085.

195. Donner A, Klar J. Design and analysis of cluster randomization trials in health research. London: Arnold; 2000.

196. Draborg E, Gyrd-Hansen D, Poulsen PB et al. International comparison of the definition and the practical application of health technology assessment. Int J Technol Assess Health Care 2005; 21(1): 89-95. https://dx.doi.org/10.1017/s0266462305050117.

197. Drazen JM. COX-2 inhibitors--a lesson in unexpected problems. N Engl J Med 2005; 352(11): 1131-1132. https://dx.doi.org/10.1056/NEJMe058038.

198. Droste S, Herrmann-Frank A, Scheibler F et al. Ethical issues in autologous stem cell transplantation (ASCT) in advanced breast cancer: a systematic literature review. BMC Med Ethics 2011; 12: 6. https://dx.doi.org/10.1186/1472-6939-12-6.

199. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996; 313(7052): 275-283. https://dx.doi.org/10.1136/bmj.313.7052.275.

200. Drummond MF, Sculpher MJ, Claxton K et al. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015.

201. Duffy S, de Kock S, Misso K et al. Supplementary searches of PubMed to improve currency of MEDLINE and MEDLINE In-Process searches via Ovid. J Med Libr Assoc 2016; 104(4): 309-312. https://dx.doi.org/10.3163/1536-5050.104.4.011.

202. Dundar Y, Dodd S, Dickson R et al. Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies. Health Technol Assess 2006; 10(5): iii-iv, ix-145. https://dx.doi.org/10.3310/hta10050.

203. Dwan K, Altman DG, Arnaiz JA et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS One 2008; 3(8): e3081. https://dx.doi.org/10.1371/journal.pone.0003081.

204. Dwan K, Gamble C, Williamson PR et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. PLoS One 2013; 8(7): e66844. https://dx.doi.org/10.1371/journal.pone.0066844.

205. Eady AM, Wilczynski NL, Haynes RB. PsycINFO search strategies identified methodologically sound therapy studies and review articles for use by clinicians and researchers. J Clin Epidemiol 2008; 61(1): 34-40. https://dx.doi.org/10.1016/j.jclinepi.2006.09.016.

206. Ebbesen M, Jensen TG, Andersen S et al. Ethical perspectives on RNA interference therapeutics. Int J Med Sci 2008; 5(3): 159-168. https://dx.doi.org/10.7150/ijms.5.159.

207. Ebell MH, Siwek J, Weiss BD et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician 2004; 69(3): 548-556.

208. Ebrahim S, Vercammen K, Sivanand A et al. Minimally Important Differences in Patient or Proxy-Reported Outcome Studies Relevant to Children: A Systematic Review. Pediatrics 2017; 139(3): e20160833. https://dx.doi.org/10.1542/peds.2016-0833.

209. Eden J, Levit L, Berg A et al. Finding what works in health care; standards for systematic reviews. Washington: National Academies Press; 2011.

210. Edwards JE, McQuay HJ, Moore RA et al. Reporting of adverse effects in clinical trials should be improved: Lessons from acute postoperative pain. J Pain Symptom Manage 1999; 18(6): 427-437. https://dx.doi.org/Doi 10.1016/S0885-3924(99)00093-7.

211. Egger M, Davey Smith G, Altman DG. Systematic reviews in health care; meta-analysis in context. London: BMJ Publishing Group; 2001.

212. Egger M, Davey Smith G, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315(7109): 629-634. https://dx.doi.org/10.1136/bmj.315.7109.629.

213. Elwyn G, Frosch D, Thomson R et al. Shared decision making: a model for clinical practice. J Gen Intern Med 2012; 27(10): 1361-1367. https://dx.doi.org/10.1007/s11606-012-2077-6.

214. Elwyn G, O'Connor A, Stacey D et al. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. BMJ 2006; 333(7565): 417. https://dx.doi.org/10.1136/bmj.38926.629329.AE.

215. Engelke K, Droste S. Bewertungen der rechtlichen Aspekte von Technologien. In: Perleth M, Busse R, Gerhardus A et al (Ed). Health Technology Assessment; Konzepte, Methoden, Praxis für Wissenschaft und Entscheidungsfindung. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2014. S. 280-296.

216. Engels EA, Schmid CH, Terrin N et al. Heterogeneity and statistical significance in meta-analysis: an empirical study of 125 meta-analyses. Stat Med 2000; 19(13): 1707-1728. https://dx.doi.org/10.1002/1097-0258(20000715)19:13<1707::aid-sim491>3.0.co;2-p.

217. Epstein RM, Alper BS, Quill TE. Communicating evidence for participatory decision making. JAMA 2004; 291(19): 2359-2366. https://dx.doi.org/10.1001/jama.291.19.2359.

218. Etzioni R, Gulati R, Mallinger L et al. Influence of study features and methods on overdiagnosis estimates in breast and prostate cancer screening. Ann Intern Med 2013; 158(11): 831-838. https://dx.doi.org/10.7326/0003-4819-158-11-201306040-00008.

219. Europäisches Parlament, Rat der Europäischen Union. Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Amtsblatt der Europäischen Gemeinschaften 2000; 43(L18): 1-5.

220. Europäisches Parlament, Rat der Europäischen Union. Verordnung (EU) 2017/745 des Europäischen Parlaments und des Rates vom 5. April 2017 über Medizinprodukte, zur Änderung der Richtlinie 2001/83/EG, der Verordnung (EG) Nr. 178/2002 und der Verordnung (EG) Nr. 1223/2009 und zur Aufhebung der Richtlinien 90/385/EWG und 93/42/EWG des Rates [online]. 2017 [Accessed: 04.02.2021]. URL: https://eur-lex.europa.eu/legal-content/DE/TXT/?uri=CELEX%3A32017R0745.

221. European Commission. Medical Devices - EUDAMED [online]. [Accessed: 05.08.2021]. URL: https://ec.europa.eu/health/md_eudamed/overview_en.

222. European Medicines Agency. Webauftritt [online]. [Accessed: 01.02.2021]. URL: https://www.ema.europa.eu/en.

223. European Medicines Agency. Points to consider on application with; 1. Meta-analyses; 2. One pivotal study [online]. 2001 [Accessed: 01.02.2021]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf.

224. European Medicines Agency. Guideline on the choice of the non-inferiority margin [online]. 2005 [Accessed: 01.02.2021]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003636.pdf.

225. European Medicines Agency. Reflection paper on the regulatory guidance for the use of Health Related Quality of Life (HRQL) measures in the evaluation of medicinal products [online]. 2005 [Accessed: 01.02.2021]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003637.pdf.

226. European Medicines Agency. Guideline on clinical trials in small populations [online]. 2006 [Accessed: 01.02.2021]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf.

227. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus; Draft [online]. 2010 [Accessed: 01.02.2021]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/02/WC500073570.pdf.

228. European Medicines Agency. Guideline on Missing Data in Confirmatory Clinical Trials [online]. 2010 [Accessed: 01.02.2021]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf.

229. European Medicines Agency. Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014 [online]. 2014 [Accessed: 01.02.2021]. URL: https://www.ema.europa.eu/en/news/posting-clinical-trial-summary-results-european-clinical-trials-database-eudract-become-mandatory.

230. European Network for Health Technology Assessment. Joint Action on HTA 2012-2015; HTA Core Model Version 3.0 [online]. 2016 [Accessed: 01.02.2021]. URL: https://eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf.

231. European Network for Health Technology Assessment. Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness [online]. 2017 [Accessed: 01.02.2021]. URL: https://www.eunethta.eu/wp-content/uploads/2018/01/Guideline_Information_Retrieval_V1-2_2017.pdf.

232. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA 1992; 268(17): 2420-2425. https://dx.doi.org/10.1001/jama.1992.03490170092032.

233. Eyding D, Lelgemann M, Grouven U et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 2010; 341: c4737. https://dx.doi.org/10.1136/bmj.c4737.

234. Facey K, Boivin A, Gracia J et al. Patients' perspectives in health technology assessment: a route to robust evidence and fair deliberation. Int J Technol Assess Health Care 2010; 26(3): 334-340. https://dx.doi.org/10.1017/S0266462310000395.

235. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 1990; 9(12): 1447-1454. https://dx.doi.org/10.1002/sim.4780091208.

236. Fayers P, Machin D. Quality of life; the assessment, analysis and interpretation of patient-reported outcomes. Chichester: Wiley; 2007.

237. Feeny D. As good as it gets but good enough for which applications? Med Decis Making 2006; 26(4): 307-309. https://dx.doi.org/10.1177/0272989X06290975.

238. Feinstein AR. Clinical epidemiology; the architecture of clinical research. Philadelphia: Saunders; 1985.

239. Feinstein AR. Invidious comparisons and unmet clinical challenges. Am J Med 1992; 92(2): 117-120. https://dx.doi.org/10.1016/0002-9343(92)90099-w.

240. Feise RJ. Do multiple outcome measures require p-value adjustment? BMC Med Res Methodol 2002; 2: 8. https://dx.doi.org/10.1186/1471-2288-2-8.

241. Feldman-Stewart D, Brennenstuhl S, Brundage MD. A purpose-based evaluation of information for patients: an approach to measuring effectiveness. Patient Educ Couns 2007; 65(3): 311-319. https://dx.doi.org/10.1016/j.pec.2006.08.012.

242. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. Health Econ 2004; 13(5): 405-415. https://dx.doi.org/10.1002/hec.903.

243. Fergusson D, Aaron SD, Guyatt G et al. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ 2002; 325(7365): 652-654. https://dx.doi.org/10.1136/bmj.325.7365.652.

244. Ferrante di Ruffano L, Hyde CJ, McCaffery KJ et al. Assessing the value of diagnostic tests: a framework for designing and evaluating trials. BMJ 2012; 344: e686. https://dx.doi.org/10.1136/bmj.e686.

245. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ 2007; 334(7597): 786. https://dx.doi.org/10.1136/bmj.39136.682083.AE.

246. Field MJ, Lohr KN. Clinical practice guidelines; directions for a new program. Washington: National Academy Press; 1990.

247. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94(446): 496-509. https://dx.doi.org/10.1080/01621459.1999.10474144.

248. Fleiss JL, Tytun A, Ury HK. A simple approximation for calculating sample sizes for comparing independent proportions. Biometrics 1980; 36(2): 343-346. https://dx.doi.org/10.2307/2529990.

249. Fleming TR. Surrogate endpoints and FDA's accelerated approval process. Health Aff (Millwood) 2005; 24(1): 67-78. https://dx.doi.org/10.1377/hlthaff.24.1.67.

250. Fleming TR. Addressing missing data in clinical trials. Ann Intern Med 2011; 154(2): 113-117. https://dx.doi.org/10.7326/0003-4819-154-2-201101180-00010.

251. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996; 125(7): 605-613. https://dx.doi.org/10.7326/0003-4819-125-7-199610010-00011.

252. Fletcher RH, Fletcher SW. Klinische Epidemiologie; Grundlagen und Anwendung. Bern: Huber; 2007.

253. Flynn TN. Using conjoint analysis and choice experiments to estimate QALY values: issues to consider. Pharmacoeconomics 2010; 28(9): 711-722. https://dx.doi.org/10.2165/11535660-000000000-00000.

254. Ford I, Norrie J. Pragmatic Trials. N Engl J Med 2016; 375(5): 454-463. https://dx.doi.org/10.1056/NEJMra1510059.

255. Forsetlund L, Kirkehei I, Harboe I et al. A comparison of two search methods for determining the scope of systematic reviews and health technology assessments. Int J Technol Assess Health Care 2012; 28(1): 59-64. https://dx.doi.org/10.1017/S0266462311000626.

256. Franken M, Heintz E, Gerber-Grote A et al. Health Economics as Rhetoric: The Limited Impact of Health Economics on Funding Decisions in Four European Countries. Value Health 2016; 19(8): 951-956. https://dx.doi.org/10.1016/j.jval.2016.08.001.

257. Freemantle N. Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic? BMJ 2001; 322: 989-991. https://dx.doi.org/10.1136/bmj.322.7292.989.

258. Freemantle N, Blonde L, Bolinder B et al. Real-world trials to answer real-world questions. Pharmacoeconomics 2005; 23(8): 747-754. https://dx.doi.org/10.2165/00019053-200523080-00001.

259. Freemantle N, Calvert M. Weighing the pros and cons for composite outcomes in clinical trials. J Clin Epidemiol 2007; 60(7): 658-659. https://dx.doi.org/10.1016/j.jclinepi.2006.10.024.

260. Friede T, Rover C, Wandel S et al. Meta-analysis of few small studies in orphan diseases. Res Synth Methods 2017; 8(1): 79-91. https://dx.doi.org/10.1002/jrsm.1217.

261. Friede T, Rover C, Wandel S et al. Meta-analysis of two studies in the presence of heterogeneity with applications in rare diseases. Biom J 2017; 59(4): 658-671. https://dx.doi.org/10.1002/bimj.201500236.

262. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991; 11(2): 88-94. https://dx.doi.org/10.1177/0272989X9101100203.

263. Furukawa TA, Guyatt GH, Griffith LE. Can we individualize the 'number needed to treat'? An empirical study of summary effect measures in meta-analyses. Int J Epidemiol 2002; 31(1): 72-76. https://dx.doi.org/10.1093/ije/31.1.72.

264. Gafni A, Birch S, Mehrez A. Economics, health and health economics: HYEs (healthy-years equivalent) versus QALYs (quality-adjusted live-year). J Health Econ 1993; 12(3): 325-339. https://dx.doi.org/10.1016/0167-6296(93)90015-7.

265. Garber AM, Weinstein MC, Torrance GW et al. Theoretical foundations of cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB et al (Ed). Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996. S. 25-53.

266. Gartlehner G, Moore CG. Direct versus indirect comparisons: a summary of the evidence. Int J Technol Assess Health Care 2008; 24(2): 170-177. https://dx.doi.org/10.1017/S0266462308080240.

267. Gehanno JF, Rollin L, Le Jean T et al. Precision and recall of search strategies for identifying studies on return-to-work in Medline. J Occup Rehabil 2009; 19(3): 223-230. https://dx.doi.org/10.1007/s10926-009-9177-0.

268. Gemeinsamer Bundesausschuss. Anlage I zum 2. Kapitel der Verfahrensordnung; Antrag zur Erprobung von Untersuchungs- und Behandlungsmethoden nach § 137e des Fünften Buches Sozialgesetzbuch (SGB V) [online]. [Accessed: 01.02.2021]. URL: https://www.g-ba.de/downloads/17-98-3627/Anlage%20I_2-Kapitel-VerfO_Erprobungsantrag_Formular_2017-12-21_iK-2018-03-28.pdf.

269. Gemeinsamer Bundesausschuss. Mindestmengenregelungen gemäß § 136b Abs. 1 Satz 1 Nr. 2 SGB V [online]. URL: https://www.g-ba.de/richtlinien/5/.

270. Gemeinsamer Bundesausschuss. Verfahrensordnung des Gemeinsamen Bundesauschusses; Anlage II zum 5. Kapitel – Format und Gliederung des Dossiers, einzureichende Unterlagen, Vorgaben für technische Standards [online]. [Accessed: 05.08.2021]. URL: https://www.g-ba.de/richtlinien/anlage/167/.

271. Gemeinsamer Bundesausschuss. Verfahrensordnung des Gemeinsamen Bundesausschusses [online]. URL: https://www.g-ba.de/informationen/richtlinien/42/.

272. Gemeinsamer Bundesausschuss. Beauftragung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen [online]. 2004 [Accessed: 01.02.2021]. URL: https://www.g-ba.de/downloads/39-261-216/2004-12-21-Generalauftrag-IQWiG.pdf.

273. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über die Anpassung der Beauftragung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen zur Erstellung von Patienteninformationen [online]. 2008 [Accessed: 01.02.2021]. URL: https://www.g-ba.de/downloads/39-261-650/2008-03-13-IQWiG-Anpassung-Generalauftrag.pdf.

274. Gemeinsamer Bundesausschuss. Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL) [online]. 2020 [Accessed: 05.08.2021]. URL: https://www.g-ba.de/downloads/62-492-2416/DMP-A-RL_2020-11-20_iK-2021-02-25.pdf.

275. Gerhardt U. Patientenkarrieren. Frankfurt am Main: Suhrkamp; 1986.

276. Gerhardus A, Stich AK. Die Bewertung sozio-kultureller Aspekte im HTA. In: Perleth M, Busse R, Gerhardus A et al (Ed). Health Technology Assessment; Konzepte, Methoden, Praxis für Wissenschaft und Entscheidungsfindung. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2014. S. 312-320.

277. Gerste B, Drogan D, Günster C. Diagnosehäufigkeit und Inanspruchnahme von Gesundheitsleistungen. In: Klauber J, Günster C, Gerste B et al (Ed). Versorgungs-Report 2015/2016. Stuttgart: Schattauer; 2016. S. 391-444.

278. Glanville JM, Duffy S, McCool R et al. Searching ClinicalTrials.gov and the International Clinical Trials Registry Platform to inform systematic reviews: what are the optimal search approaches? J Med Libr Assoc 2014; 102(3): 177-183. https://dx.doi.org/10.3163/1536-5050.102.3.007.

279. Glasziou P, Chalmers I, Rawlins M et al. When are randomised trials unnecessary? Picking signal from noise. BMJ 2007; 334(7589): 349-351. https://dx.doi.org/10.1136/bmj.39070.527986.68.

280. Glasziou P, Vandenbroucke JP, Chalmers I. Assessing the quality of research. BMJ 2004; 328(7430): 39-41. https://dx.doi.org/10.1136/bmj.328.7430.39.

281. Glasziou PP, Sanders SL. Investigating causes of heterogeneity in systematic reviews. Stat Med 2002; 21(11): 1503-1511. https://dx.doi.org/10.1002/sim.1183.

282. Glenton C, Nilsen ES, Carlsen B. Lay perceptions of evidence-based information--a qualitative evaluation of a website for back pain sufferers. BMC Health Serv Res 2006; 6: 34. https://dx.doi.org/10.1186/1472-6963-6-34.

283. Godwin M, Ruhland L, Casson I et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC Med Res Methodol 2003; 3: 28. https://dx.doi.org/10.1186/1471-2288-3-28.

284. Goldacre B, Drysdale H, Dale A et al. COMPare: a prospective cohort study correcting and monitoring 58 misreported trials in real time. Trials 2019; 20(1): 118. https://dx.doi.org/10.1186/s13063-019-3173-2.

285. Goldacre B, Drysdale H, Marston C et al. COMPare: Qualitative analysis of researchers' responses to critical correspondence on a cohort of 58 misreported trials. Trials 2019; 20(1): 124. https://dx.doi.org/10.1186/s13063-019-3172-3.

286. Gonnermann A, Framke T, Grosshennig A et al. No solution yet for combining two independent studies in the presence of heterogeneity. Stat Med 2015; 34(16): 2476-2480. https://dx.doi.org/10.1002/sim.6473.

287. Gonnermann A, Kottas M, Koch A. Biometrische Entscheidungsunterstützung in Zulassung und Nutzenbewertung am Beispiel der Implikationen von heterogenen Ergebnissen in Untergruppen der Studienpopulation. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2015; 58(3): 274-282. https://dx.doi.org/10.1007/s00103-014-2105-2.

288. Goossen K, Tenckhoff S, Probst P et al. Optimal literature search for systematic reviews in surgery. Langenbecks Arch Surg 2018; 403(1): 119-129. https://dx.doi.org/10.1007/s00423-017-1646-x.

289. Gøtzsche PC, Liberati A, Torri V et al. Beware of surrogate outcome measures. Int J Technol Assess Health Care 1996; 12(2): 238-246. https://dx.doi.org/10.1017/s0266462300009594.

290. Graf von der Schulenburg JM, Greiner W, Jost F et al. Deutsche Empfehlungen zur gesundheitsökonomischen Evaluation - dritte und aktualisierte Fassung des Hannoveraner Konsens. Gesundheitsökonomie & Qualitätsmanagement 2007; 12(5): 285-290. https://dx.doi.org/10.1055/s-2007-963505.

291. Graham RM, Mancher M, Miller-Wolman D et al. Clinical practice guidelines we can trust [online]. 2011 [Accessed: 05.02.2021]. URL: http://www.awmf.org/fileadmin/user_upload/Leitlinien/International/IOM_CPG_lang_2011.pdf.

292. Gray JAM. How to get better value healthcare. Oxford: Offox Press; 2007.

293. Greenhalgh T, Hurwitz B. Narrative based medicine: why study narrative? BMJ 1999; 318(7175): 48-50. https://dx.doi.org/10.1136/bmj.318.7175.48.

294. Greenland S, Morgenstern H. Ecological bias, confounding, and effect modification. Int J Epidemiol 1989; 18(1): 269-274. https://dx.doi.org/10.1093/ije/18.1.269.

295. Greiner W, Damm O. Die Berechnung von Kosten und Nutzen. In: Schöffski O, Graf von der Schulenburg JM (Ed). Gesundheitsökonomische Evaluationen. Berlin: Springer; 2012. S. 23-42.

296. Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet 2002; 359(9300): 57-61. https://dx.doi.org/10.1016/S0140-6736(02)07283-5.

297. Grimes DA, Schulz KF. Surrogate end points in clinical research: hazardous to your health. Obstet Gynecol 2005; 105(5 Pt 1): 1114-1118. https://dx.doi.org/10.1097/01.AOG.0000157445.67309.19.

298. Gu Y, Norman R, Viney R. Estimating health state utility values from discrete choice experiments--a QALY space model approach. Health Econ 2014; 23(9): 1098-1114. https://dx.doi.org/10.1002/hec.3066.

299. Guddat C, Grouven U, Bender R et al. A note on the graphical presentation of prediction intervals in random-effects meta-analyses. Syst Rev 2012; 1: 34. https://dx.doi.org/10.1186/2046-4053-1-34.

300. Guolo A, Varin C. Random-effects meta-analysis: the number of studies matters. Stat Methods Med Res 2017; 26(3): 1500-1518. https://dx.doi.org/10.1177/0962280215583568.

301. Guyatt G, Rennie D, Meade MO et al. Users' guides to the medical literature; a manual for evidence-based clinical practice. New York: McGraw-Hill Education; 2015.

302. Guyatt G, Sackett D, Taylor DW et al. Determining optimal therapy--randomized trials in individual patients. N Engl J Med 1986; 314(14): 889-892. https://dx.doi.org/10.1056/NEJM198604033141406.

303. Guyatt GH. Evidence-based medicine. ACP J Club 1991; 114(2): A16. https://dx.doi.org/10.7326/ACPJC-1991-114-2-A16.

304. Guyatt GH, Jaeschke R, Roberts R. N-of-1 randomized clinical trials in pharmacoepidemiology. In: Strom BL (Ed). Pharmacoepidemiology. Chichester: Wiley; 2005. S. 665-680.

305. Guyatt GH, Oxman AD, Kunz R et al. Going from evidence to recommendations. BMJ 2008; 336(7652): 1049-1051. https://dx.doi.org/10.1136/bmj.39493.646875.AE.

306. Guyatt GH, Oxman AD, Kunz R et al. What is "quality of evidence" and why is it important to clinicians? BMJ 2008; 336(7651): 995-998. https://dx.doi.org/10.1136/bmj.39490.551019.BE.

307. Guyatt GH, Oxman AD, Sultan S et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011; 64(12): 1311-1316. https://dx.doi.org/10.1016/j.jclinepi.2011.06.004.

308. Guyatt GH, Oxman AD, Vist G et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol 2011; 64(4): 407-415. https://dx.doi.org/10.1016/j.jclinepi.2010.07.017.

309. Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336(7650): 924-926. https://dx.doi.org/10.1136/bmj.39489.470347.AD.

310. Guyatt GH, Sackett DL, Sinclair JC et al. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA 1995; 274(22): 1800-1804. https://dx.doi.org/10.1001/jama.274.22.1800.

311. Guyatt GH, Tugwell PX, Feeny DH et al. The role of before-after studies of therapeutic impact in the evaluation of diagnostic technologies. J Chronic Dis 1986; 39(4): 295-304. https://dx.doi.org/10.1016/0021-9681(86)90051-2.

312. Hall AE, Chowdhury S, Hallowell N et al. Implementing risk-stratified screening for common cancers: a review of potential ethical, legal and social issues. J Public Health (Oxf) 2014; 36(2): 285-291. https://dx.doi.org/10.1093/pubmed/fdt078.

313. Halladay CW, Trikalinos TA, Schmid IT et al. Using data sources beyond PubMed has a modest impact on the results of systematic reviews of therapeutic interventions. J Clin Epidemiol 2015; 68(9): 1076-1084. https://dx.doi.org/10.1016/j.jclinepi.2014.12.017.

314. Hamza TH, van Houwelingen HC, Heijenbrok-Kal MH et al. Associating explanatory variables with summary receiver operating characteristic curves in diagnostic meta-analysis. J Clin Epidemiol 2009; 62(12): 1284-1291. https://dx.doi.org/10.1016/j.jclinepi.2009.02.002.

315. Hao Q, Devji T, Zeraatkar D et al. Minimal important differences for improvement in shoulder condition patient-reported outcomes: a systematic review to inform a BMJ Rapid Recommendation. BMJ Open 2019; 9(2): e028777. https://dx.doi.org/10.1136/bmjopen-2018-028777.

316. Harbord RM, Whiting P, Sterne JA et al. An empirical comparison of methods for meta-analysis of diagnostic accuracy showed hierarchical models are necessary. J Clin Epidemiol 2008; 61(11): 1095-1103. https://dx.doi.org/10.1016/j.jclinepi.2007.09.013.

317. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ 2001; 323(7308): 334-336. https://dx.doi.org/10.1136/bmj.323.7308.334.

318. Harden A, Garcia J, Oliver S et al. Applying systematic review methods to studies of people's views: an example from public health research. J Epidemiol Community Health 2004; 58(9): 794-800. https://dx.doi.org/10.1136/jech.2003.014829.

319. Hardt JL, Metzendorf MI, Meerpohl JJ. Surgical trials and trial registers: a cross-sectional study of randomized controlled trials published in journals requiring trial registration in the author instructions. Trials 2013; 14: 407. https://dx.doi.org/10.1186/1745-6215-14-407.

320. Harrell FE Jr. Regression modeling strategies; with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001.

321. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996; 15(4): 361-387. https://dx.doi.org/10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4.

322. Harris J. QALYfying the value of life. J Med Ethics 1987; 13(3): 117-123. https://dx.doi.org/10.1136/jme.13.3.117.

323. Harris RP, Helfand M, Woolf SH et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001; 20(3 Suppl): 21-35. https://dx.doi.org/10.1016/s0749-3797(01)00261-6.

324. Hart D. Der regulatorische Rahmen der Nutzenbewertung: Vom Arzneimittelrecht zum HTA-Recht. Medizinrecht 2004; 22(9): 469-481. https://dx.doi.org/10.1007/s00350-004-1243-1.

325. Hart D. Leitlinien und Haftungsrecht - Inkorporation, Rezeption und Wissensbasis in Wissenschaft und Praxis. In: Hart D (Ed). Klinische Leitlinien und Recht. Baden-Baden: Nomos; 2005. S. 81-103.

326. Hartling L, Featherstone R, Nuspl M et al. The contribution of databases to the results of systematic reviews: a cross-sectional study. BMC Med Res Methodol 2016; 16(1): 127. https://dx.doi.org/10.1186/s12874-016-0232-1.

327. Hartling L, Featherstone R, Nuspl M et al. Grey literature in systematic reviews: a cross-sectional study of the contribution of non-English reports, unpublished studies and dissertations to the results of meta-analyses in child-relevant reviews. BMC Med Res Methodol 2017; 17(1): 64. https://dx.doi.org/10.1186/s12874-017-0347-z.

328. Hartung J. An alternative method for meta-analysis. Biom J 1999; 41(8): 901-916. https://dx.doi.org/10.1002/(SICI)1521-4036(199912)41:8<901::AID-BIMJ901>3.0.CO;2-W.

329. Hausner E. Problems encountered with ICTRP Search Portal (comment on: "Van Enst WA et al. Identification of additional trials in prospective trial registers for Cochrane systematic reviews. PLoS One 2012; 7(8): e42812") [online]. 2014 [Accessed: 01.02.2021]. URL: https://journals.plos.org/plosone/article/comment?id=info:doi/10.1371/annotation/5aac3b1b-56ed-43bf-a07e-cb38afd31478.

330. Hausner E, Ebrahim S, Herrmann-Frank A et al. Study selection by means of a web-based Trial Selection DataBase (webTSDB) [online]. 2011 [Accessed: 01.02.2021]. URL: https://abstracts.cochrane.org/2011-madrid/study-selection-means-web-based-trial-selection-database-webtsdb.

331. Hausner E, Guddat C, Hermanns T et al. Development of search strategies for systematic reviews: validation showed the noninferiority of the objective approach. J Clin Epidemiol 2015; 68(2): 191-199. https://dx.doi.org/10.1016/j.jclinepi.2014.09.016.

332. Hausner E, Metzendorf MI, Richter B et al. Study filters for non-randomized studies of interventions consistently lacked sensitivity upon external validation. BMC Med Res Methodol 2018; 18(1): 171. https://dx.doi.org/10.1186/s12874-018-0625-4.

333. Hausner E, Waffenschmidt S. Value of using different search approaches [online]. 2019 [Accessed: 01.02.2021]. URL: http://vortal.htai.org/?q=node/993.

334. Hausner E, Waffenschmidt S, Kaiser T et al. Routine development of objectively derived search strategies. Syst Rev 2012; 1: 19. https://dx.doi.org/10.1186/2046-4053-1-19.

335. Haute Autorité de Santé. Choices in Methods for Economic Evaluation [online]. 2012 [Accessed: 01.02.2021]. URL: http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-10/choices_in_methods_for_economic_evaluation.pdf.

336. Haute Autorité de Santé. Choices in methods for economic evaluation – HAS [online]. 2020 [Accessed: 06.08.2021]. URL: https://www.has-sante.fr/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=p_3216041.

337. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006; 144(6): 427-437. https://dx.doi.org/10.7326/0003-4819-144-6-200603210-00010.

338. Hayden JA, van der Windt DA, Cartwright JL et al. Assessing bias in studies of prognostic factors. Ann Intern Med 2013; 158(4): 280-286. https://dx.doi.org/10.7326/0003-4819-158-4-201302190-00009.

339. Hayes MJ, Kaestner V, Mailankody S et al. Most medical practices are not parachutes: a citation analysis of practices felt by biomedical authors to be analogous to parachutes. CMAJ Open 2018; 6(1): E31-E38. https://dx.doi.org/10.9778/cmajo.20170088.

340. Haynes RB. Forming research questions. J Clin Epidemiol 2006; 59(9): 881-886. https://dx.doi.org/10.1016/j.jclinepi.2006.06.006.

341. Haynes RB, Cotoi C, Holland J et al. Second-order peer review of the medical literature for clinical practitioners. JAMA 2006; 295(15): 1801-1808. https://dx.doi.org/10.1001/jama.295.15.1801.

342. Haynes RB, Devereaux PJ, Guyatt GH. Clinical expertise in the era of evidence-based medicine and patient choice. BMJ Evid Based Med 2002; 7(2): 36-38. https://dx.doi.org/10.1136/ebm.7.2.36.

343. Heres S, Davis J, Maino K et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 2006; 163(2): 185-194. https://dx.doi.org/10.1176/appi.ajp.163.2.185.

344. Herxheimer A, McPherson A, Miller R et al. Database of patients' experiences (DIPEx): a multi-media approach to sharing experiences and information. Lancet 2000; 355(9214): 1540-1543. https://dx.doi.org/10.1016/S0140-6736(00)02174-7.

345. Hessel F, Kohlmann T, Krauth C et al. Gesundheitsökonomische Evaluation in der Rehabilitation; Teil I: Prinzipien und Empfehlungen für die Leistungserfassung. In: Verband Deutscher Rentenversicherungsträger (Ed). Förderschwerpunkt "Rehabilitationswissenschaften"; Empfehlungen der Arbeitsgruppen "Generische Methoden", "Routinedaten" und "Reha-Ökonomie". Frankfurt am Main: Verband Deutscher Rentenversicherungsträger; 1999. S. 106-193.

346. Higgins JP, Ramsay C, Reeves BC et al. Issues relating to study design and risk of bias when including non-randomized studies in systematic reviews on the effects of interventions. Res Synth Methods 2013; 4(1): 12-25. https://dx.doi.org/10.1002/jrsm.1056.

347. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21(11): 1539-1558. https://dx.doi.org/10.1002/sim.1186.

348. Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414): 557-560. https://dx.doi.org/10.1136/bmj.327.7414.557.

349. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009; 172(1): 137-159. https://dx.doi.org/10.1111/j.1467-985X.2008.00552.x.

350. Higgins JPT, Savović J, Page MJ et al. Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J et al (Ed). Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley-Blackwell; 2019. S. 205-228.

351. Higgins JPT, Thomas J, Chandler J et al. Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley-Blackwell; 2019.

352. Hill AB. Controlled clinical trials. Oxford: Blackwell; 1960.

353. Hingorani AD, Windt DA, Riley RD et al. Prognosis research strategy (PROGRESS) 4: stratified medicine research. BMJ 2013; 346: e5793. https://dx.doi.org/10.1136/bmj.e5793.

354. Hoaglin DC, Hawkins N, Jansen JP et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health 2011; 14(4): 429-437. https://dx.doi.org/10.1016/j.jval.2011.01.011.

355. Hoffmann-Esser W, Siering U, Neugebauer EAM et al. Systematic review of current guideline appraisals performed with the Appraisal of Guidelines for Research & Evaluation II instrument-a third of AGREE II users apply a cut-off for guideline quality. J Clin Epidemiol 2018; 95: 120-127. https://dx.doi.org/10.1016/j.jclinepi.2017.12.009.

356. Hofmann B. Toward a procedure for integrating moral issues in health technology assessment. Int J Technol Assess Health Care 2005; 21(3): 312-318. https://dx.doi.org/10.1017/s0266462305050415.

357. Hofmann B, Droste S, Oortwijn W et al. Harmonization of ethics in health technology assessment: a revision of the Socratic approach. Int J Technol Assess Health Care 2014; 30(1): 3-9. https://dx.doi.org/10.1017/S0266462313000688.

358. Hofmann B, Haustein D, Landeweerd L. Smart-Glasses: Exposing and Elucidating the Ethical Issues. Sci Eng Ethics 2017; 23(3): 701-721. https://dx.doi.org/10.1007/s11948-016-9792-z.

359. Hofmann B, Lysdahl KB, Droste S. Evaluation of ethical aspects in health technology assessment: more methods than applications? Expert Rev Pharmacoecon Outcomes Res 2015; 15(1): 5-7. https://dx.doi.org/10.1586/14737167.2015.990886.

360. Holmes-Rovner M. International Patient Decision Aid Standards (IPDAS): beyond decision aids to usual design of patient education materials. Health Expect 2007; 10(2): 103-107. https://dx.doi.org/10.1111/j.1369-7625.2007.00445.x.

361. Hopewell S, Clarke M, Askie L. Reporting of trials presented in conference abstracts needs to be improved. J Clin Epidemiol 2006; 59(7): 681-684. https://dx.doi.org/10.1016/j.jclinepi.2005.09.016.

362. Hosmer DW, Taber S, Lemeshow S. The importance of assessing the fit of logistic regression models: a case study. Am J Public Health 1991; 81(12): 1630-1635. https://dx.doi.org/10.2105/ajph.81.12.1630.

363. Hoyer A, Hirt S, Kuss O. Meta-analysis of full ROC curves using bivariate time-to-event models for interval-censored data. Res Synth Methods 2018; 9(1): 62-72. https://dx.doi.org/10.1002/jrsm.1273.

364. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13. https://dx.doi.org/10.1186/1471-2288-5-13.

365. Hummel M, IJzerman M. The past and future of the AHP in health care decision making [online]. [Accessed: 01.02.2021]. URL: https://www.isahp.org/uploads/71_0111_hummel.pdf.

366. Hummel MJM, Steuten LMG, Groothuis-Oudshoorn KGM et al. How the Analytic Hierarchy Process May Fill Missing gaps in Early Decision Modeling. ISPOR Connections 2011; 17(3): 9-10.

367. Hung HMJ, ONeill RT, Bauer P et al. The behavior of the P-value when the alternative hypothesis is true. Biometrics 1997; 53(1): 11-22.

368. Husereau D, Drummond M, Petrou S et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Pharmacoeconomics 2013; 31(5): 361-367. https://dx.doi.org/10.1007/s40273-013-0032-y.

369. Hutton B, Salanti G, Caldwell DM et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015; 162(11): 777-784. https://dx.doi.org/10.7326/M14-2385.

370. ICH E1 Expert Working Group. ICH harmonised tripartite guideline: the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions; E1; current step 4 version [online]. 1994 [Accessed: 18.03.2015]. URL: https://database.ich.org/sites/default/files/E1_Guideline.pdf.

371. ICH E9 Expert Working Group. ICH harmonised tripartite guideline: statistical principles for clinical trials. Stat Med 1999; 18(15): 1905-1942.

372. Inan H. Measuring the success of your website; a customer-centric approach to website management. Frenchs Forest: Pearson Education Australia; 2002.

373. Institut für Arbeitsmarkt- und Berufsforschung. Aktuelle Ergebnisse [online]. [Accessed: 05.08.2021]. URL: http://www.iab.de/de/befragungen/stellenangebot/aktuelle-ergebnisse.aspx.

374. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vereinbarung über die vertrauliche Behandlung von Unterlagen [online]. 2005 [Accessed: 17.02.2021]. URL: https://www.iqwig.de/download/IQWiG-VFA-Mustervertrag.pdf.

375. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Entwicklung und Anwendung von Modellen zur Berechnung von Schwellenwerten bei Mindestmengen für die Koronarchirurgie; Vorbericht [online]. 2006 [Accessed: 01.02.2021]. URL: https://www.iqwig.de/download/b05-01b_vorbericht_entwicklung_und_anwendung_von_modellen_zur_berechnung_von_schwellenwerten_bei_mindestmengen_fuer_die_koronarchirurgie.pdf.

376. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Zusammenhang zwischen Menge der erbrachten Leistungen und der Ergebnisqualität für die „Perkutane Transluminale Coronare Angieplastie (PTCA)“; Abschlussbericht [online]. 2006 [Accessed: 01.02.2021]. URL: https://www.iqwig.de/download/q05-01b_abschlussbericht_zusammenhang_menge_erbrachter_leistung_und_ergebnisqualitaet_bei_ptca.pdf.

377. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Bupropion, Mirtazapin und Reboxetin bei der Behandlung von Depression; Abschlussbericht [online]. 2009 [Accessed: 01.02.2021]. URL: https://www.iqwig.de/download/a05-20c_abschlussbericht_bupropion_mirtazapin_und_reboxetin_bei_depressionen.pdf.

378. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Aussagekraft von Surrogatendpunkten in der Onkologie; Rapid Report [online]. 2011 [Accessed: 01.02.2021]. URL: https://www.iqwig.de/download/a10-05_rapid_report_version_1-1_surrogatendpunkte_in_der_onkologie.pdf.

379. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ticagrelor – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2011 [Accessed: 01.02.2021]. URL: https://www.iqwig.de/download/a11-02_ticagrelor_nutzenbewertung_35a_sgb_v_.pdf.

380. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Suchen in Studienregistern nach Studien zu neu zugelassenen Arzneimitteln; Arbeitspapier [online]. 2016 [Accessed: 01.02.2021]. URL: https://www.iqwig.de/download/ga14-01_arbeitspapier_suchen-in-studienregistern-nach-studien-zu-neu-zugelassenen-arzneimitteln.pdf.

381. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 09.02.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_dwa-entwurf-fuer-version-6-0_v1-0.pdf.

382. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V; Rapid Report [online]. 2020 [Accessed: 01.02.2021]. URL: https://www.iqwig.de/download/A19-43_Versorgungsnahe-Daten-zum-Zwecke-der-Nutzenbewertung_Rapid-Report_V1-1.pdf.

383. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Örtlich begrenzter Prostatakrebs [online]. 2020 [Accessed: 05.08.2021]. URL: https://www.gesundheitsinformation.de/oertlich-begrenzter-prostatakrebs.html.

384. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Datenschutzerklärung; Gesundheitsinformation.de [online]. 2021 [Accessed: 05.08.2021]. URL: https://www.gesundheitsinformation.de/service/datenschutz/.

385. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Webauftritt [online]. [Accessed: 18.03.2015]. URL: https://www.ich.org/.

386. International Society for Pharmacoeconomics and Outcomes Research. Good Practices Reports & More [online]. [Accessed: 05.08.2021]. URL: https://www.ispor.org/heor-resources/good-practices.

387. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol 2014; 14: 25. https://dx.doi.org/10.1186/1471-2288-14-25.

388. Ioannidis JP, Evans SJ, Gotzsche PC et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004; 141(10): 781-788. https://dx.doi.org/10.7326/0003-4819-141-10-200411160-00009.

389. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. JAMA 2001; 285(4): 437-443. https://dx.doi.org/10.1001/jama.285.4.437.

390. Ioannidis JP, Mulrow CD, Goodman SN. Adverse events: the more you search, the more you find. Ann Intern Med 2006; 144(4): 298-300. https://dx.doi.org/10.7326/0003-4819-144-4-200602210-00013.

391. Irmen L, Linner U. Die Repräsentation generisch maskuliner Personenbezeichnungen; eine theoretische Integration bisheriger Befunde. Z Psychol 2005; 213(3): 167-175. https://dx.doi.org/10.1026/0044-3409.213.3.167.

392. Irwig L, Tosteson AN, Gatsonis C et al. Guidelines for meta-analyses evaluating diagnostic tests. Ann Intern Med 1994; 120(8): 667-676. https://dx.doi.org/10.7326/0003-4819-120-8-199404150-00008.

393. Jackson D. The power of the standard test for the presence of heterogeneity in meta-analysis. Stat Med 2006; 25(15): 2688-2699. https://dx.doi.org/10.1002/sim.2481.

394. Jackson D, Law M, Rücker G et al. The Hartung-Knapp modification for random-effects meta-analysis: A useful refinement but are there any residual concerns? Stat Med 2017; 36(25): 3923-3934. https://dx.doi.org/10.1002/sim.7411.

395. Jackson D, Turner R. Power analysis for random-effects meta-analysis. Res Synth Methods 2017; 8(3): 290-302. https://dx.doi.org/10.1002/jrsm.1240.

396. Jackson N, Waters E. Criteria for the systematic review of health promotion and public health interventions. Health Promot Int 2005; 20(4): 367-374. https://dx.doi.org/10.1093/heapro/dai022.

397. Jadad AR. Randomized Controlled Trials: Questions, Answers, and Musings. Malden: Blackwell Publishing; 2007.

398. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. CMAJ 1997; 156(10): 1411-1416.

399. Jadad AR, Enkin MW. Randomized controlled trials; questions, answers and musings. Malden: Blackwell Publishing; 2007.

400. Jansen JP, Fleurence R, Devine B et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health 2011; 14(4): 417-428. https://dx.doi.org/10.1016/j.jval.2011.04.002.

401. Jansen JP, Trikalinos T, Cappelleri JC et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health 2014; 17(2): 157-173. https://dx.doi.org/10.1016/j.jval.2014.01.004.

402. Janzen T, Hausner E, Waffenschmidt S. Entwicklung und Evaluation von RCT- und SR-Filtern für die Suche nach nicht verschlagworteten Datensätzen in PubMed [online]. 2013 [Accessed: 01.02.2021]. URL: http://www.egms.de/static/de/meetings/ebm2013/13ebm059.shtml.

403. Jayadevappa R, Cook R, Chhatre S. Minimal important difference to infer changes in health-related quality of life-a systematic review. J Clin Epidemiol 2017; 89: 188-198. https://dx.doi.org/10.1016/j.jclinepi.2017.06.009.

404. Jenuwine ES, Floyd JA. Comparison of Medical Subject Headings and text-word searches in MEDLINE to retrieve studies on sleep in healthy individuals. J Med Libr Assoc 2004; 92(3): 349-353.

405. Jiao S, Tsutani K, Haga N. Review of Cochrane reviews on acupuncture: how Chinese resources contribute to Cochrane reviews. J Altern Complement Med 2013; 19(7): 613-621. https://dx.doi.org/10.1089/acm.2012.0113.

406. Johannesson M. Avoiding double-counting in pharmacoeconomic studies. Pharmacoeconomics 1997; 11(5): 385-388. https://dx.doi.org/10.2165/00019053-199711050-00001.

407. Johnson RF. Sample size issues for conjoint analysis. In: Orme BK (Ed). Getting started with conjoint analysis; strategies for product design and pricing research. Madison: Research Publishers LLC; 2010. S. 57-66.

408. Johnston BC, Ebrahim S, Carrasco-Labra A et al. Minimally important difference estimates and methods: a protocol. BMJ Open 2015; 5(10): e007953. https://dx.doi.org/10.1136/bmjopen-2015-007953.

409. Jones B, Jarvis P, Lewis JA et al. Trials to assess equivalence: the importance of rigorous methods. BMJ 1996; 313(7048): 36-39. https://dx.doi.org/10.1136/bmj.313.7048.36.

410. Jones B, Kenward MG. Design and analysis of cross-over trials. Boca Raton: CRC Press; 2015.

411. Jones CW, Keil LG, Holland WC et al. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. BMC Med 2015; 13: 282. https://dx.doi.org/10.1186/s12916-015-0520-3.

412. Jones HE, Gatsonsis CA, Trikalinos TA et al. Quantifying how diagnostic test accuracy depends on threshold in a meta-analysis. Stat Med 2019; 38(24): 4789-4803. https://dx.doi.org/10.1002/sim.8301.

413. Jull A, Bennett D. Do n-of-1 trials really tailor treatment? Lancet 2005; 365(9476): 1992-1994. https://dx.doi.org/10.1016/S0140-6736(05)66678-0.

414. Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ 2001; 323(7303): 42-46. https://dx.doi.org/10.1136/bmj.323.7303.42.

415. Juszczak E, Altman DG, Hopewell S et al. Reporting of Multi-Arm Parallel-Group Randomized Trials: Extension of the CONSORT 2010 Statement. JAMA 2019; 321(16): 1610-1620. https://dx.doi.org/10.1001/jama.2019.3087.

416. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. Hoboken: Wiley-Interscience; 2002.

417. Kass PH, Gold EB. Modern epidemiologic study designs. In: Ahrens W, Pigeot I (Ed). Handbook of epidemiology. Berlin: Springer; 2005. S. 321-344.

418. Kastner M, Wilczynski NL, Walker-Dilks C et al. Age-specific search strategies for Medline. J Med Internet Res 2006; 8(4): e25. https://dx.doi.org/10.2196/jmir.8.4.e25.

419. Katrak P, Bialocerkowski AE, Massy-Westropp N et al. A systematic review of the content of critical appraisal tools. BMC Med Res Methodol 2004; 4: 22. https://dx.doi.org/10.1186/1471-2288-4-22.

420. Katz MH. Multivariable analysis: a primer for readers of medical research. Ann Intern Med 2003; 138(8): 644-650. https://dx.doi.org/10.7326/0003-4819-138-8-200304150-00012.

421. Kettunen T, Liimatainen L, Villberg J et al. Developing empowering health counseling measurement. Preliminary results. Patient Educ Couns 2006; 64(1-3): 159-166. https://dx.doi.org/10.1016/j.pec.2005.12.012.

422. Kickbusch IS. Health literacy: addressing the health and education divide. Health Promot Int 2001; 16(3): 289-297. https://dx.doi.org/10.1093/heapro/16.3.289.

423. Kiefer C, Sturtz S, Bender R. Indirect comparisons and network meta-analyses: estimation of effects in the absence of head-to-head trials—part 22 of a series on evaluation of scientific publications. Dtsch Arztebl Int 2015; 112(47): 803-808. https://dx.doi.org/10.3238/arztebl.2015.0803.

424. Kiefer C, Sturtz S, Bender R. A simulation study to compare different estimation approaches for network meta-analysis and corresponding methods to evaluate the consistency assumption. BMC Med Res Methodol 2020; 20(1): 36. https://dx.doi.org/10.1186/s12874-020-0917-3.

425. Kieser M, Hauschke D. Assessment of clinical relevance by considering point estimates and associated confidence intervals. Pharm Stat 2005; 4(2): 101-107. https://dx.doi.org/10.1002/pst.161.

426. Kieser M, Röhmel J, Friede T. Power and sample size determination when assessing the clinical relevance of trial results by 'responder analyses'. Stat Med 2004; 23(21): 3287-3305. https://dx.doi.org/10.1002/sim.1910.

427. Kleinbaum DG, Klein M. Survival analysis; a self-learning text. New York: Springer; 2005.

428. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Stat Med 2003; 22(17): 2693-2710. https://dx.doi.org/10.1002/sim.1482.

429. Knelangen M, Hausner E, Metzendorf MI et al. Trial registry searches for randomized controlled trials of new drugs required registry-specific adaptation to achieve adequate sensitivity. J Clin Epidemiol 2018; 94: 69-75. https://dx.doi.org/10.1016/j.jclinepi.2017.11.003.

430. Knottnerus JA, Bouter LM. The ethics of sample size: two-sided testing and one-sided thinking. J Clin Epidemiol 2001; 54(2): 109-110. https://dx.doi.org/10.1016/s0895-4356(00)00276-6.

431. Köbberling J. Der Zweifel als Triebkraft des Erkenntnisgewinns in der Medizin. In: Kunz R, Ollenschläger G, Raspe H et al (Ed). Lehrbuch evidenzbasierte Medizin in Klinik und Praxis. Köln: Deutscher Ärzteverlag; 2007. S. 3-14.

432. Koch A, Ziegler S. Metaanalyse als Werkzeug zum Erkenntnisgewinn. Med Klin (Munich) 2000; 95(2): 109-116. https://dx.doi.org/10.1007/BF03044996.

433. Koch K, Waltering A. IQWiG-Gesundheitsinformation: Pragmatischer Weg zum Themenkatalog. Dtsch Arztebl Ausg A 2016; 113(11): A489-A493.

434. Köhler M, Haag S, Biester K et al. Information on new drugs at market entry: retrospective analysis of health technology assessment reports versus regulatory reports, journal publications, and registry reports. BMJ 2015; 350: h796. https://dx.doi.org/10.1136/bmj.h796.

435. Kolman J, Meng P, Scott G. Good clinical practice; standard operating procedures for clinical researchers. Chichester: Wiley; 1998.

436. Kommission der Europäischen Gemeinschaften. Richtlinie 2003/63/EG der Kommission vom 25. Juni 2003 zur Änderung der Richtlinie 2001/83/EG des Europäischen Parlaments und des Rates zur Schaffung eines Gemeinschaftskodexes für Humanarzneimittel. Amtsblatt der Europäischen Gemeinschaften 2003; 46(L159): 46-94.

437. Koopmanschap MA, Rutten FF, van Ineveld BM et al. The friction cost method for measuring indirect costs of disease. J Health Econ 1995; 14(2): 171-189. https://dx.doi.org/10.1016/0167-6296(94)00044-5.

438. Kraemer HC, Frank E, Kupfer DJ. Moderators of treatment outcomes: clinical, research, and policy importance. JAMA 2006; 296(10): 1286-1289. https://dx.doi.org/10.1001/jama.296.10.1286.

439. Krankheitserfahrungen.de. Webauftritt [online]. [Accessed: 01.02.2021]. URL: https://www.krankheitserfahrungen.de/.

440. Kreis J, Puhan MA, Schünemann HJ et al. Consumer involvement in systematic reviews of comparative effectiveness research. Health Expect 2013; 16(4): 323-337. https://dx.doi.org/10.1111/j.1369-7625.2011.00722.x.

441. Kristensen FB, Sigmund H. Health technology assessment handbook [online]. 2008 [Accessed: 05.02.2021]. URL: https://www.sst.dk/~/media/ECAAC5AA1D6943BEAC96907E03023E22.ashx.

442. Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? Eur J Epidemiol 2004; 19(8): 751-760. https://dx.doi.org/10.1023/b:ejep.0000036568.02655.f8.

443. Krug S. Don't make me think! Web Usability; das intuitive Web. Heidelberg: mitp; 2006.

444. Kulbe A. Grundwissen Psychologie, Soziologie und Pädagogik; Lehrbuch für Pflegeberufe. Stuttgart: Kohlhammer; 2009.

445. Kunz R, Djulbegovic B, Schunemann HJ et al. Misconceptions, challenges, uncertainty, and progress in guideline recommendations. Semin Hematol 2008; 45(3): 167-175. https://dx.doi.org/10.1053/j.seminhematol.2008.04.005.

446. Kuss O. Statistical methods for meta-analyses including information from studies without any events-add nothing to nothing and succeed nevertheless. Stat Med 2015; 34(7): 1097-1116. https://dx.doi.org/10.1002/sim.6383.

447. Laaser U, Hurrelmann K. Gesundheitsförderung und Krankheitsprävention. In: Hurrelmann K, Laaser U (Ed). Handbuch Gesundheitswissenschaften. Weinheim: Juventa Verlag; 1998. S. 395-424.

448. Lacny S, Wilson T, Clement F et al. Kaplan-Meier survival analysis overestimates cumulative incidence of health-related events in competing risk settings: a meta-analysis. J Clin Epidemiol 2018; 93: 25-35. https://dx.doi.org/10.1016/j.jclinepi.2017.10.006.

449. Lange S, Freitag G. Choice of delta: requirements and reality--results of a systematic review. Biom J 2005; 47(1): 12-27. https://dx.doi.org/10.1002/bimj.200410085.

450. Lange S, Sauerland S, Lauterberg J et al. The Range and Scientific Value of Randomized Trials. Dtsch Arztebl Int 2017; 114(38): 635-640. https://dx.doi.org/10.3238/arztebl.2017.0635.

451. Lapsley P. The patient's journey: travelling through life with a chronic illness. BMJ 2004; 329: 582. https://dx.doi.org/10.1136/bmj.329.7466.582.

452. Lavis JN. How can we support the use of systematic reviews in policymaking? PLoS Med 2009; 6(11): e1000141. https://dx.doi.org/10.1371/journal.pmed.1000141.

453. Law AM. How to build valid and credible simulation models. In: Mason SJ, Hill RR, Mönch L et al (Ed). Proceedings of the 2008 Winter Simulation Conference. Piscataway: IEEE; 2008. S. 39-47.

454. Law AM. Simulation modeling and analysis. New York: McGraw-Hill Education; 2015.

455. Lee ET, Wang JW. Statistical methods for survival data analysis. Hoboken: Wiley-Interscience; 2003.

456. Leeflang MM, Deeks JJ, Gatsonis C et al. Systematic reviews of diagnostic test accuracy. Ann Intern Med 2008; 149(12): 889-897. https://dx.doi.org/10.7326/0003-4819-149-12-200812160-00008.

457. Lefebvre C, Glanville J, Briscoe S et al. Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J et al (Ed). Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley-Blackwell; 2019. S. 67-107.

458. Leidl R, Graf von der Schulenburg JM, Wasem J. Ansätze und Methoden der ökonomischen Evaluation - eine internationale Perspektive [online]. 1999 [Accessed: 09.02.2021]. URL: https://portal.dimdi.de/de/hta/hta_berichte/hta009_bericht_de.pdf.

459. Lewin S, Booth A, Glenton C et al. Applying GRADE-CERQual to qualitative evidence synthesis findings: introduction to the series. Implement Sci 2018; 13(Suppl 1): 2. https://dx.doi.org/10.1186/s13012-017-0688-3.

460. Lewin S, Glenton C, Munthe-Kaas H et al. Using qualitative evidence in decision making for health and social interventions: an approach to assess confidence in findings from qualitative evidence syntheses (GRADE-CERQual). PLoS Med 2015; 12(10): e1001895. https://dx.doi.org/10.1371/journal.pmed.1001895.

461. Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. BMJ 2001; 322(7300): 1479-1480. https://dx.doi.org/10.1136/bmj.322.7300.1479.

462. Leys M. Health care policy: qualitative evidence and health technology assessment. Health Policy 2003; 65(3): 217-226. https://dx.doi.org/10.1016/s0168-8510(02)00209-9.

463. Liberati A, Sheldon TA, Banta HD. EUR-ASSESS Project Subgroup report on Methodology. Methodological guidance for the conduct of health technology assessment. Int J Technol Assess Health Care 1997; 13(2): 186-219. https://dx.doi.org/10.1017/s0266462300010369.

464. Lieb K, Klemperer D, Koch K et al. Interessenskonflikt in der Medizin; mit Transparenz Vertrauen stärken. Dtsch Arztebl Ausg A 2011; 108(6): A256-A260.

465. Lijmer JG, Bossuyt PM. Various randomized designs can be used to evaluate medical tests. J Clin Epidemiol 2009; 62(4): 364-373. https://dx.doi.org/10.1016/j.jclinepi.2008.06.017.

466. Lijmer JG, Mol BW, Heisterkamp S et al. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA 1999; 282(11): 1061-1066. https://dx.doi.org/10.1001/jama.282.11.1061.

467. Lipscomb J, Drummond M, Fryback D et al. Retaining, and enhancing, the QALY. Value Health 2009; 12 Suppl 1(Suppl 1): S18-26. https://dx.doi.org/10.1111/j.1524-4733.2009.00518.x.

468. Lipscomb J, Weinstein MC, Torrance GW. Time preference. In: Gold MR, Siegel JE, Russell LB et al (Ed). Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996. S. 214-246.

469. Little RJA, Rubin DB. Statistical analysis with missing data. Hoboken: Wiley; 2002.

470. Lo B, Field MJ. Conflict of interest in medical research, education, and practice. Washington: National Academies Press; 2009.

471. Lockwood C, Munn Z, Porritt K. Qualitative research synthesis: methodological guidance for systematic reviewers utilizing meta-aggregation. Int J Evid Based Healthc 2015; 13(3): 179-187. https://dx.doi.org/10.1097/XEB.0000000000000062.

472. Lord SJ, Irwig L, Simes RJ. When is measuring sensitivity and specificity sufficient to evaluate a diagnostic test, and when do we need randomized trials? Ann Intern Med 2006; 144(11): 850-855. https://dx.doi.org/10.7326/0003-4819-144-11-200606060-00011.

473. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004; 23(20): 3105-3124. https://dx.doi.org/10.1002/sim.1875.

474. Lu G, Ades AE, Sutton AJ et al. Meta-analysis of mixed treatment comparisons at multiple follow-up times. Stat Med 2007; 26(20): 3681-3699. https://dx.doi.org/10.1002/sim.2831.

475. Lu GB, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. J Am Stat Assoc 2006; 101(474): 447-459. https://dx.doi.org/10.1198/016214505000001302.

476. Luce BR, Manning WG, Siegel JE et al. Estimating costs in cost-effectiveness analysis. In: Gold MR, Russell LB, Siegel JE et al (Ed). Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996. S. 176-213.

477. Lühnen J, Albrecht M, Mühlhauser I et al. Leitlinie evidenzbasierte Gesundheitsinformation [online]. 2017 [Accessed: 01.02.2021]. URL: https://www.ebm-netzwerk.de/de/medien/pdf/leitlinie-evidenzbasierte-gesundheitsinformation-fin.pdf.

478. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med 2002; 21(16): 2313-2324. https://dx.doi.org/10.1002/sim.1201.

479. Lysdahl KB, Mozygemba K, Burns L et al. Guidance for assessing effectiveness, economic aspects, ehtical aspects, socio-cultural aspects and legal aspects in complex technologies [online]. 2016 [Accessed: 05.02.2021]. URL: http://www.integrate-hta.eu/wp-content/uploads/2016/08/IPP_Guidance-INTEGRATE-HTA_Nr.3_FINAL.pdf.

480. Lysdahl KB, Oortwijn W, van der Wilt GJ et al. Ethical analysis in HTA of complex health interventions. BMC Med Ethics 2016; 17: 16. https://dx.doi.org/10.1186/s12910-016-0099-z.

481. Macaskill P, Gatsonis C, Deeks JJ et al. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy; Chapter 10 Analysing and Presenting Results [online]. 2010 [Accessed: 01.02.2021]. URL: https://methods.cochrane.org/sites/methods.cochrane.org.sdt/files/public/uploads/Chapter%2010%20-%20Version%201.0.pdf.

482. MacDermid JC, Brooks D, Solway S et al. Reliability and validity of the AGREE instrument used by physical therapists in assessment of clinical practice guidelines. BMC Health Serv Res 2005; 5(1): 18. https://dx.doi.org/10.1186/1472-6963-5-18.

483. Maetzel A. Der Gebrauch von Nutzwerten im gesundheitsökonomischen Vergleich von Interventionen bei verschiedenen Krankheitsbildern; eine Einfuhrung. Z Rheumatol 2004; 63(5): 380-384. https://dx.doi.org/10.1007/s00393-004-0658-4.

484. Malterud K. The art and science of clinical knowledge: evidence beyond measures and numbers. Lancet 2001; 358(9279): 397-400. https://dx.doi.org/10.1016/S0140-6736(01)05548-9.

485. Mandelblatt JS, Fryback DG, Weinstein MC et al. Assessing the effectiveness of health interventions. In: Gold MR, Siegel JE, Russell LB et al (Ed). Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996. S. 135-175.

486. Mandrekar SJ, Sargent DJ. Clinical trial designs for predictive biomarker validation: theoretical considerations and practical challenges. J Clin Oncol 2009; 27(24): 4027-4034. https://dx.doi.org/10.1200/JCO.2009.22.3701.

487. Mandrekar SJ, Sargent DJ. All-comers versus enrichment design strategy in phase II trials. J Thorac Oncol 2011; 6(4): 658-660. https://dx.doi.org/10.1097/JTO.0b013e31820e17cb.

488. Mangiapane S, Velasco Garrido M. Surrogatendpunkte als Parameter der Nutzenbewertung [online]. 2009 [Accessed: 01.02.2021]. URL: https://portal.dimdi.de/de/hta/hta_berichte/hta250_bericht_de.pdf.

489. Marsh K, Lanitis T, Neasham D et al. Assessing the value of healthcare interventions using multi-criteria decision analysis: a review of the literature. Pharmacoeconomics 2014; 32(4): 345-365. https://dx.doi.org/10.1007/s40273-014-0135-0.

490. Marshall IJ, Noel-Storr A, Kuiper J et al. Machine learning for identifying Randomized Controlled Trials: An evaluation and practitioner's guide. Res Synth Methods 2018; 9(4): 602-614. https://dx.doi.org/10.1002/jrsm.1287.

491. Martin LP, Arias-Gallo J, Perez-Chrzanowska H et al. Transfusion Requirements in Microsurgical Reconstruction in Maxillofacial Surgery: Ethical and Legal Problems of Patients Who Are Jehovah's Witnesses. Craniomaxillofac Trauma Reconstr 2013; 6(1): 31-36. https://dx.doi.org/10.1055/s-0033-1333828.

492. Martini P. Methodenlehre der therapeutischen Untersuchung. Berlin: Springer; 1932.

493. Mathes T, Kuss O. A comparison of methods for meta-analysis of a small number of studies with binary outcomes. Res Synth Methods 2018; 9(3): 366-381. https://dx.doi.org/10.1002/jrsm.1296.

494. Matthias K, Gruber S, Pietsch B. Evidenz von Volume-Outcome-Beziehungen und Mindestmengen: Diskussion in der aktuellen Literatur. Gesundheits- und Sozialpolitik 2014; 68(3): 23-30. https://dx.doi.org/10.5771/1611-5821-2014-3-23.

495. Mattke S, Kelley E, Scherer P et al. Health Care Quality Indicators Project: Initial Indicators Report [online]. 2006 [Accessed: 01.02.2021]. URL: http://dx.doi.org/10.1787/481685177056.

496. Mauskopf JA, Earnshaw S, Mullins CD. Budget impact analysis: review of the state of the art. Expert Rev Pharmacoecon Outcomes Res 2005; 5(1): 65-79. https://dx.doi.org/10.1586/14737167.5.1.65.

497. Mauskopf JA, Sullivan SD, Annemans L et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. Value Health 2007; 10(5): 336-347. https://dx.doi.org/10.1111/j.1524-4733.2007.00187.x.

498. Mc Gowan J, Sampson M, Salzwedel DM et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Explanation and Elaboration (PRESS E&E) [online]. 2016 [Accessed: 01.02.2021]. URL: https://www.cadth.ca/sites/default/files/pdf/CP0015_PRESS_Update_Report_2016.pdf.

499. McAlister FA, Straus SE, Sackett DL et al. Analysis and reporting of factorial trials: a systematic review. JAMA 2003; 289(19): 2545-2553. https://dx.doi.org/10.1001/jama.289.19.2545.

500. McCulloch P, Taylor I, Sasako M et al. Randomised trials in surgery: problems and possible solutions. BMJ 2002; 324(7351): 1448-1451. https://dx.doi.org/10.1136/bmj.324.7351.1448.

501. McGauran N, Wieseler B, Kreis J et al. Reporting bias in medical research - a narrative review. Trials 2010; 11: 37. https://dx.doi.org/10.1186/1745-6215-11-37.

502. McGregor M, Caro JJ. QALYs: are they helpful to decision makers? Pharmacoeconomics 2006; 24(10): 947-952. https://dx.doi.org/10.2165/00019053-200624100-00002.

503. McInnes MDF, Moher D, Thombs BD et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA 2018; 319(4): 388-396. https://dx.doi.org/10.1001/jama.2017.19163.

504. McShane LM, Altman DG, Sauerbrei W et al. Reporting recommendations for tumor marker prognostic studies (REMARK). J Natl Cancer Inst 2005; 97(16): 1180-1184. https://dx.doi.org/10.1093/jnci/dji237.

505. Merlin T, Lehman S, Hiller JE et al. The "linked evidence approach" to assess medical tests: a critical analysis. Int J Technol Assess Health Care 2013; 29(3): 343-350. https://dx.doi.org/10.1017/S0266462313000287.

506. Moher D, Hopewell S, Schulz KF et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c869. https://dx.doi.org/10.1136/bmj.c869.

507. Moher D, Pham B, Lawson ML et al. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. Health Technol Assess 2003; 7(41): 1-90. https://dx.doi.org/10.3310/hta7410.

508. Moher D, Shamseer L, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015; 4: 1. https://dx.doi.org/10.1186/2046-4053-4-1.

509. Möhler R. Qualitative Evidenzsynthesen - Methodologien, Methoden und Herausforderungen. QuPuG 2016; 3(2): 70-77.

510. Molenberghs G, Burzykowski T, Alonso A et al. A unified framework for the evaluation of surrogate endpoints in mental-health clinical trials. Stat Methods Med Res 2010; 19(3): 205-236. https://dx.doi.org/10.1177/0962280209105015.

511. Molnar FJ, Man-Son-Hing M, Fergusson D. Systematic review of measures of clinical significance employed in randomized controlled trials of drugs for dementia. J Am Geriatr Soc 2009; 57(3): 536-546. https://dx.doi.org/10.1111/j.1532-5415.2008.02122.x.

512. Moons KG, Altman DG, Reitsma JB et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015; 162(1): W1-73. https://dx.doi.org/10.7326/M14-0698.

513. Morrison A, Polisena J, Husereau D et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care 2012; 28(2): 138-144. https://dx.doi.org/10.1017/S0266462312000086.

514. Mozygemba K, Hofmann B, Lysdal KB et al. Guidance to assess socio-cultural aspects [online]. 2016 [Accessed: 17.02.2021]. URL: http://www.integrate-hta.eu/wp-content/uploads/2016/08/IPP_Guidance-INTEGRATE-HTA_Nr.3_FINAL.pdf.

515. Mühlbacher A, Bethge S, Tockhorn A. Präferenzmessung im Gesundheitswesen: Grundlagen von Discrete-Choice-Experimenten. Gesundheitsökonomie & Qualitätsmanagement 2013; 18(04): 159-172. https://dx.doi.org/10.1055/s-0032-1330500.

516. Mullan RJ, Flynn DN, Carlberg B et al. Systematic reviewers commonly contact study authors but do so with limited rigor. J Clin Epidemiol 2009; 62(2): 138-142. https://dx.doi.org/10.1016/j.jclinepi.2008.08.002.

517. Müllner M, Matthews H, Altman DG. Reporting on statistical methods to adjust for confounding: a cross-sectional survey. Ann Intern Med 2002; 136(2): 122-126. https://dx.doi.org/10.7326/0003-4819-136-2-200201150-00009.

518. Munn Z, Porritt K, Lockwood C et al. Establishing confidence in the output of qualitative research synthesis: the ConQual approach. BMC Med Res Methodol 2014; 14: 108. https://dx.doi.org/10.1186/1471-2288-14-108.

519. Murphy E, Dingwall R, Greatbatch D et al. Qualitative research methods in health technology assessment: a review of the literature. Health Technol Assess 1998; 2(16): iii-ix, 1-274.

520. National Advisory Committee on Health and Disability. Screening to Improve Health in New Zealand; Criteria to assess screening programmes [online]. 2003 [Accessed: 05.02.2021]. URL: https://www.nsu.govt.nz/system/files/resources/screening_to_improve_health.pdf.

521. National Health and Medical Research Council. Cultural competency in health: a guide for policy, partnerships and participation [online]. 2006 [Accessed: 05.02.2021]. URL: https://www.nhmrc.gov.au/file/2771/download?token=H3v1MEBC.

522. National Institute for Health and Care Excellence. Guidance and advice list: interventional procedures guidance [online]. [Accessed: 01.02.2021]. URL: https://www.nice.org.uk/guidance/indevelopment?type=ipg.

523. National Institute for Health and Care Excellence. Guide to the processes of technology appraisal [online]. 2014 [Accessed: 05.02.2021]. URL: https://www.nice.org.uk/process/pmg19/resources/guide-to-the-processes-of-technology-appraisal-pdf-72286663351237.

524. National Institutes of Health, Department of Health and Human Services. Clinical trials registration and results information submission; final rule. Fed Regist 2016; 81(183): 64981-65157.

525. Neidhardt K, Wasmuth T, Schmid A. Die Gewichtung multipler patientenrelevanter Endpunkte: ein methodischer Vergleich von Conjoint Analyse und Analytic Hierarchy Process unter Berücksichtigung des Effizienzgrenzenkonzepts des IQWiG; Diskussionspapier [online]. 2012 [Accessed: 05.11.2019]. URL: http://www.fiwi.uni-bayreuth.de/de/download/WP_02-12.pdf.

526. Newcombe RG, Bender R. Implementing GRADE: calculating the risk difference from the baseline risk and the relative risk. Evid Based Med 2014; 19(1): 6-8. https://dx.doi.org/10.1136/eb-2013-101340.

527. Nielsen J, Loranger H. Web Usability. München: Addison-Wesley; 2008.

528. Nilsen ES, Myrhaug HT, Johansen M et al. Methods of consumer involvement in developing healthcare policy and research, clinical practice guidelines and patient information material. Cochrane Database Syst Rev 2006; (3): CD004563. https://dx.doi.org/10.1002/14651858.CD004563.pub2.

529. Nord E. An alternative to QALYs: the saved young life equivalent (SAVE). BMJ 1992; 305(6858): 875-877. https://dx.doi.org/10.1136/bmj.305.6858.875.

530. Nord E. Cost-value analysis in health care; making sense out of QALYs. Cambridge: Cambridge University Press; 1999.

531. Nordin A, Taft C, Lundgren-Nilsson A et al. Minimal important differences for fatigue patient reported outcome measures-a systematic review. BMC Med Res Methodol 2016; 16: 62. https://dx.doi.org/10.1186/s12874-016-0167-6.

532. Nüesch E, Jüni P. Commentary: Which meta-analyses are conclusive? Int J Epidemiol 2009; 38(1): 298-303. https://dx.doi.org/10.1093/ije/dyn265.

533. Nutbeam D. Health promotion glossary. Health Promot Int 1998; 13(4): 349-364. https://dx.doi.org/10.1093/heapro/13.4.349.

534. O'Mahony JF, Paulden M. NICE's selective application of differential discounting: ambiguous, inconsistent, and unjustified. Value Health 2014; 17(5): 493-496. https://dx.doi.org/10.1016/j.jval.2013.02.014.

535. O'Neill RT. Statistical analyses of adverse event data from clinical trials. Special emphasis on serious events. Drug Inf J 1987; 21(1): 9-20. https://dx.doi.org/10.1177/009286158702100104.

536. O'Neill RT. Assessment of safety. In: Peace KE (Ed). Biopharmaceutical statistics for drug development. New York: Dekker; 1988. S. 543-604.

537. OCEBM Levels of Evidence Working Group. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence [online]. 2011 [Accessed: 15.11.2021]. URL: https://www.cebm.ox.ac.uk/files/levels-of-evidence/cebm-levels-of-evidence-2-1.pdf.

538. Odgaard-Jensen J, Vist GE, Timmer A et al. Randomisation to protect against selection bias in healthcare trials. Cochrane Database Syst Rev 2011; (4): MR000012. https://dx.doi.org/10.1002/14651858.MR000012.pub3.

539. Oliver A. A normative perspective on discounting health outcomes. J Health Serv Res Policy 2013; 18(3): 186-189. https://dx.doi.org/10.1177/1355819613485671.

540. Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. Pharmacoeconomics 2002; 20(7): 443-454. https://dx.doi.org/10.2165/00019053-200220070-00002.

541. Organisation for Economic Co-operation and Development. OECD Secretary-General's Report to Ministers 2021 [online]. 2021 [Accessed: 05.08.2021]. URL: https://www.oecd-ilibrary.org/deliver/8cd95b77-en.pdf.

542. Orlewska E, Mierzejewski P. Proposal of Polish guidelines for conducting financial analysis and their comparison to existing guidance on budget impact in other countries. Value Health 2004; 7(1): 1-10. https://dx.doi.org/10.1111/j.1524-4733.2004.71257.x.

543. Ousmen A, Touraine C, Deliu N et al. Distribution- and anchor-based methods to determine the minimally important difference on patient-reported outcome questionnaires in oncology: a structured review. Health Qual Life Outcomes 2018; 16(1): 228. https://dx.doi.org/10.1186/s12955-018-1055-z.

544. Oxman AD, Guyatt GH. Guidelines for reading literature reviews. CMAJ 1988; 138(8): 697-703.

545. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. J Clin Epidemiol 1991; 44(11): 1271-1278. https://dx.doi.org/10.1016/0895-4356(91)90160-b.

546. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. Ann Intern Med 1992; 116(1): 78-84. https://dx.doi.org/10.7326/0003-4819-116-1-78.

547. Oxman AD, Guyatt GH, Singer J et al. Agreement among reviewers of review articles. J Clin Epidemiol 1991; 44(1): 91-98. https://dx.doi.org/10.1016/0895-4356(91)90205-N.

548. Page MJ, Higgins JPT, Sterne JAC. Assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J et al (Ed). Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley-Blackwell; 2019. S. 349-374.

549. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. https://dx.doi.org/10.1136/bmj.n71.

550. Page MJ, Moher D, Bossuyt PM et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021; 372: n160. https://dx.doi.org/10.1136/bmj.n160.

551. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998; 17(24): 2815-2834. https://dx.doi.org/10.1002/(sici)1097-0258(19981230)17:24<2815::aid-sim110>3.0.co;2-8.

552. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med 1980; 302(20): 1109-1117. https://dx.doi.org/10.1056/NEJM198005153022003.

553. Paulden M, Claxton K. Budget allocation and the revealed social rate of time preference for health. Health Econ 2012; 21(5): 612-618. https://dx.doi.org/10.1002/hec.1730.

554. Paynter R, Banez LL, Berliner E et al. EPC Methods: An Exploration of the Use of TextMining Software in Systematic Reviews [online]. 2016 [Accessed: 01.02.2021]. URL: https://www.ncbi.nlm.nih.gov/books/NBK362044/pdf/Bookshelf_NBK362044.pdf.

555. Perleth M, Busse R, Gerhardus A et al. Health Technology Assessment; Konzepte, Methoden, Praxis für Wissenschaft und Entscheidungsfindung. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2014.

556. Perleth M, Gibis B, Velasco Garrido M et al. Organisationsstrukturen und Qualität. In: Perleth M, Busse R, Gerhardus A et al (Ed). Health Technology Assessment; Konzepte, Methoden, Praxis für Wissenschaft und Entscheidungsfindung. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2014. S. 265-280.

557. Perleth M, Jakubowski E, Busse R. What is 'best practice' in health care? State of the art and perspectives in improving the effectiveness and efficiency of the European health care systems. Health Policy 2001; 56(3): 235-250. https://dx.doi.org/10.1016/s0168-8510(00)00138-x.

558. Petitti DB, Teutsch SM, Barton MB et al. Update on the methods of the U.S. Preventive Services Task Force: insufficient evidence. Ann Intern Med 2009; 150(3): 199-205. https://dx.doi.org/10.7326/0003-4819-150-3-200902030-00010.

559. Petkova E, Tarpey T, Huang L et al. Interpreting meta-regression: application to recent controversies in antidepressants' efficacy. Stat Med 2013; 32(17): 2875-2892. https://dx.doi.org/10.1002/sim.5766.

560. Philips Z, Ginnelly L, Sculpher M et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004; 8(36): iii-iv, ix-xi, 1-158. https://dx.doi.org/10.3310/hta8360.

561. Piaggio G, Elbourne DR, Pocock SJ et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA 2012; 308(24): 2594-2604. https://dx.doi.org/10.1001/jama.2012.87802.

562. Pieper D, Jülich F, Antoine SL et al. Studies analysing the need for health-related information in Germany - a systematic review. BMC Health Serv Res 2015; 15: 407. https://dx.doi.org/10.1186/s12913-015-1076-9.

563. Platt RW, Leroux BG, Breslow N. Generalized linear mixed models for meta-analysis. Stat Med 1999; 18(6): 643-654. https://dx.doi.org/10.1002/(sici)1097-0258(19990330)18:6<643::aid-sim76>3.0.co;2-m.

564. Pocock SJ. Clinical trials; a practical approach. Chichester: Wiley; 1983.

565. Pranic S, Marusic A. Changes to registration elements and results in a cohort of Clinicaltrials.gov trials were not reflected in published articles. J Clin Epidemiol 2016; 70: 26-37. https://dx.doi.org/10.1016/j.jclinepi.2015.07.007.

566. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989; 8(4): 431-440. https://dx.doi.org/10.1002/sim.4780080407.

567. Provalis Research. WordStat: content analysis and text mining software [online]. [Accessed: 01.02.2021]. URL: https://provalisresearch.com/products/content-analysis-software/.

568. Public Health England. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme [online]. 2015 [Accessed: 01.02.2021]. URL: https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme.

569. Puhan MA, Singh S, Weiss CO et al. A framework for organizing and selecting quantitative approaches for benefit-harm assessment. BMC Med Res Methodol 2012; 12: 173. https://dx.doi.org/10.1186/1471-2288-12-173.

570. Putter H, Schumacher M, van Houwelingen HC. On the relation between the cause-specific hazard and the subdistribution rate for competing risks data: The Fine-Gray model revisited. Biom J 2020; 62(3): 790-807. https://dx.doi.org/10.1002/bimj.201800274.

571. Raftery J. How should we value future health? Was NICE right to change? Value Health 2013; 16(5): 699-700. https://dx.doi.org/10.1016/j.jval.2013.03.001.

572. Raum E, Perleth M. Methoden der Metaanalyse von diagnostischen Genauigkeitsstudien [online]. 2003 [Accessed: 01.02.2021]. URL: http://portal.dimdi.de/de/hta/hta_berichte/hta025_bericht_de.pdf.

573. Reitsma JB, Glas AS, Rutjes AW et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005; 58(10): 982-990. https://dx.doi.org/10.1016/j.jclinepi.2005.02.022.

574. Relevo R, Balshem H. Evidence for Comparing Medical Interventions [online]. 2011 [Accessed: 01.02.2021]. URL: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-finding-evidence_methods.pdf.

575. Rethlefsen ML, Kirtley S, Waffenschmidt S et al. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021; 10(1): 39. https://dx.doi.org/10.1186/s13643-020-01542-z.

576. Revicki D, Hays RD, Cella D et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008; 61(2): 102-109. https://dx.doi.org/10.1016/j.jclinepi.2007.03.012.

577. Reynen E, Robson R, Ivory J et al. A retrospective comparison of systematic reviews with same-topic rapid reviews. J Clin Epidemiol 2018; 96: 23-34. https://dx.doi.org/10.1016/j.jclinepi.2017.12.001.

578. Rice M, Ali MU, Fitzpatrick-Lewis D et al. Testing the effectiveness of simplified search strategies for updating systematic reviews. J Clin Epidemiol 2017; 88: 148-153. https://dx.doi.org/10.1016/j.jclinepi.2017.06.005.

579. Richardson J, Khan MA, Iezzi A et al. Cross-national comparison of twelve quality of life instruments; MIC Paper 5; Canada [online]. 2012 [Accessed: 05.02.2021]. URL: https://www.aqol.com.au/papers/researchpaper82.pdf.

580. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011; 342: d549. https://dx.doi.org/10.1136/bmj.d549.

581. Ringbaek T, Brondum E, Martinez G et al. EuroQoL in assessment of the effect of pulmonary rehabilitation COPD patients. Respir Med 2008; 102(11): 1563-1567. https://dx.doi.org/10.1016/j.rmed.2008.06.016.

582. Robinson KA, Whitlock EP, O'Neil ME et al. Integration of Existing Systematic Reviews. Research White Paper (Prepared by the Scientific Resource Center under Contract No. 290-2012-00004-C) [online]. 2014 [Accessed: 01.02.2021]. URL: https://www.ncbi.nlm.nih.gov/sites/books/NBK216379/pdf/Bookshelf_NBK216379.pdf.

583. Rockwood K, Fay S, Song X et al. Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. CMAJ 2006; 174(8): 1099-1105. https://dx.doi.org/10.1503/cmaj.051432.

584. Roebruck P, Elze M, Hauschke D et al. Literaturübersicht zur Fallzahlplanung für Äquivalenzprobleme. Inform Biom Epidemiol Med Biol 1997; 28(2): 51-63.

585. Röhmel J, Hauschke D, Koch A et al. Biometrische Verfahren zum Wirksamkeitsnachweis im Zulassungsverfahren; Nicht-Unterlegenheit in klinischen Studien. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2005; 48(5): 562-571. https://dx.doi.org/10.1007/s00103-005-1042-5.

586. Rosenthal JA. Qualitative Descriptors of Strength of Association and Effect Size. J Soc Serv Res 1996; 21(4): 37-59. 37. https://dx.doi.org/10.1300/J079v21n04_02.

587. Ross SM. Simulation. San Diego: Academic Press; 2013.

588. Rossouw JE. Estrogens for prevention of coronary heart disease. Putting the brakes on the bandwagon. Circulation 1996; 94(11): 2982-2985. https://dx.doi.org/10.1161/01.cir.94.11.2982.

589. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet 2005; 365(9454): 176-186. https://dx.doi.org/10.1016/S0140-6736(05)17709-5.

590. Röver C, Knapp G, Friede T. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. BMC Med Res Methodol 2015; 15: 99. https://dx.doi.org/10.1186/s12874-015-0091-1.

591. Royall RM. The Effect of Sample-Size on the Meaning of Significance Tests. Am Stat 1986; 40(4): 313-315. https://dx.doi.org/10.1080/00031305.1986.10475424.

592. Royle P, Bain L, Waugh N. Systematic reviews of epidemiology in diabetes: finding the evidence. BMC Med Res Methodol 2005; 5: 2. https://dx.doi.org/10.1186/1471-2288-5-2.

593. Royle P, Waugh N. Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system. Health Technol Assess 2003; 7(34): iii, ix-x, 1-51. https://dx.doi.org/10.3310/hta7340.

594. Royston P. A strategy for modelling the effect of a continuous covariate in medicine and epidemiology. Stat Med 2000; 19(14): 1831-1847. https://dx.doi.org/10.1002/1097-0258(20000730)19:14<1831::aid-sim502>3.0.co;2-1.

595. Royston P, Altman DG. Regression Using Fractional Polynomials of Continuous Covariates: Parsimonious Parametric Modeling. J R Stat Soc Ser C Appl Stat 1994; 43(3): 429-467. https://dx.doi.org/10.2307/2986270.

596. Rücker G. Network meta-analysis, electrical networks and graph theory. Res Synth Methods 2012; 3(4): 312-324. https://dx.doi.org/10.1002/jrsm.1058.

597. Rücker G, Schwarzer G, Carpenter J et al. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. Stat Med 2009; 28(5): 721-738. https://dx.doi.org/10.1002/sim.3511.

598. Russell LB, Siegen JE, Daniels N et al. Cost-effectiveness analysis as a guide to resource allocation in health: roles and limitations. In: Gold MR, Siegel JE, Russell LB et al (Ed). Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996. S. 3-24.

599. Ryan M, Gerard K, Amaya-Amaya M. Using discrete choice experiments to value health and health care. Dordrecht: Springer; 2008.

600. Saaty T, Vargas LG. Decision making with the analytic network process; economic, political, social and technological applications with benefits, opportunities, costs and risks. New York: Springer; 2013.

601. Saaty TL. A scaling method for priorities in hierarchical structures. J Math Psychol 1977; 15(3): 234-281. https://dx.doi.org/10.1016/0022-2496(77)90033-5.

602. Saaty TL. Decision making with the Analytic Hierarchy Process. International Journal of Services Sciences 2008; 1(1): 83-98. https://dx.doi.org/10.1504/IJSSci.2008.01759.

603. Saaty TL. Theory and applications of the analytic network process; decision making with benefits, opportunities, costs, and risks. Pittsburgh: RWS Publications; 2009.

604. Saaty TL, Vargas LG. The Analytic Hierarchy Process: wash criteria should not be ignored. International Journal of Management and Decision Making 2006; 7(2/3): 180-188. https://dx.doi.org/10.1504/IJMDM.2006.009142.

605. Sachverständigenrat für die Konzertierte Aktion im Gesundheitswesen. Bedarfsgerechtigkeit und Wirtschaftlichkeit; Band III; Über- Unter- und Fehlversorgung; Gutachten 2000/2001; ausführliche Zusammenfassung [online]. 2001 [Accessed: 05.08.2021]. URL: https://www.svr-gesundheit.de/fileadmin/Gutachten/Gutachten_2000_2001/Kurzfassung_Band3.pdf.

606. Sackett DL. Bias in analytic research. J Chronic Dis 1979; 32(1-2): 51-63. https://dx.doi.org/10.1016/0021-9681(79)90012-2.

607. Sackett DL, Rosenberg WM, Gray JA et al. Evidence based medicine: what it is and what it isn't. BMJ 1996; 312(7023): 71-72. https://dx.doi.org/10.1136/bmj.312.7023.71.

608. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods 2012; 3(2): 80-97. https://dx.doi.org/10.1002/jrsm.1037.

609. Salanti G, Higgins JP, Ades AE et al. Evaluation of networks of randomized trials. Stat Methods Med Res 2008; 17(3): 279-301. https://dx.doi.org/10.1177/0962280207080643.

610. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. J Clin Epidemiol 2009; 62(8): 857-864. https://dx.doi.org/10.1016/j.jclinepi.2008.10.001.

611. Sampson M. Should meta-analysts search Embase in addition to Medline? J Clin Epidemiol 2003; 56(10): 943-955. https://dx.doi.org/10.1016/s0895-4356(03)00110-0.

612. Sampson M, McGowan J. Errors in search strategies were identified by type and frequency. J Clin Epidemiol 2006; 59(10): 1057-1063. https://dx.doi.org/10.1016/j.jclinepi.2006.01.007.

613. Sampson M, McGowan J. Inquisitio validus Index Medicus: A simple method of validating MEDLINE systematic review searches. Res Synth Methods 2011; 2(2): 103-109. https://dx.doi.org/10.1002/jrsm.40.

614. Sampson M, McGowan J, Cogo E et al. An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 2009; 62(9): 944-952. https://dx.doi.org/10.1016/j.jclinepi.2008.10.012.

615. Sampson M, McGowan J, Lefebvre C et al. PRESS: Peer Review of Electronic Search Strategies [online]. 2008 [Accessed: 05.02.2021]. URL: http://www.cadth.ca/media/pdf/477_PRESS-Peer-Review-Electronic-Search-Strategies_tr_e.pdf.

616. Sampson M, McGowan J, Tetzlaff J et al. No consensus exists on search reporting methods for systematic reviews. J Clin Epidemiol 2008; 61(8): 748-754. https://dx.doi.org/10.1016/j.jclinepi.2007.10.009.

617. Sampson MJ. Updating Searches for Systematic Reviews [online]. 2009 [Accessed: 05.02.2021]. URL: https://pure.aber.ac.uk/portal/files/10374343/Sampson_Updating_Searches_for_Systematic_Reviews_PhD.pdf.

618. Sargent DJ, Conley BA, Allegra C et al. Clinical trial designs for predictive marker validation in cancer treatment trials. J Clin Oncol 2005; 23(9): 2020-2027. https://dx.doi.org/10.1200/JCO.2005.01.112.

619. Sargent DJ, Mandrekar SJ. Statistical issues in the validation of prognostic, predictive, and surrogate biomarkers. Clin Trials 2013; 10(5): 647-652. https://dx.doi.org/10.1177/1740774513497125.

620. Sargent RG. Verification and validation of simulation models. In: Johansson B, Jain S, Montoya-Torres J et al (Ed). Proceedings of the 2010 Winter Simulation Conference. Piscataway: IEEE; 2010. S. 166-183.

621. SAS Institute. SAS/STAT 9.2 User's Guide; Second Edition [online]. 2009 [Accessed: 01.02.2021]. URL: http://support.sas.com/documentation/cdl/en/statug/63033/PDF/default/statug.pdf.

622. Sauerbrei W, Royston P. Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials. J R Stat Soc Ser A Stat Soc 1999; 162(1): 71-94. https://dx.doi.org/10.1111/1467-985x.00122.

623. Sauerland S, Fujita-Rohwerder N, Zens Y et al. Premarket evaluation of medical devices: a cross-sectional analysis of clinical studies submitted to a German ethics committee. BMJ Open 2019; 9(2): e027041. https://dx.doi.org/10.1136/bmjopen-2018-027041.

624. Sawaya GF, Guirguis-Blake J, LeFevre M et al. Update on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit. Ann Intern Med 2007; 147(12): 871-875. https://dx.doi.org/10.7326/0003-4819-147-12-200712180-00007.

625. Sayers A. Tips and tricks in performing a systematic review. Br J Gen Pract 2007; 57(545): 999. https://dx.doi.org/10.3399/096016407782604938.

626. Schlosser RW, Wendt O, Bhavnani S et al. Use of information-seeking strategies for developing systematic reviews and engaging in evidence-based practice: the application of traditional and comprehensive Pearl Growing. A review. Int J Lang Commun Disord 2006; 41(5): 567-582. https://dx.doi.org/10.1080/13682820600742190.

627. Schluter PJ, Ware RS. Single patient (n-of-1) trials with binary treatment preference. Stat Med 2005; 24(17): 2625-2636. https://dx.doi.org/10.1002/sim.2132.

628. Schmoor C, Schumacher M, Finke J et al. Competing risks and multistate models. Clin Cancer Res 2013; 19(1): 12-21. https://dx.doi.org/10.1158/1078-0432.CCR-12-1619.

629. Schöffski O. Grundformen gesundheitsökonomischer Evaluationen. In: Schöfski O, Graf von der Schulenburg JM (Ed). Gesundheitsökonomische Evaluationen. Berlin: Springer; 2012. S. 43-70.

630. Schöffski O, Graf von der Schulenburg JM. Gesundheitsökonomische Evaluationen. Berlin: Springer; 2012.

631. Schulz A, Schürmann C, Skipka G et al. Performing Meta-analyses with Very Few Studies. In: Evangelou V, Veroniki AA (Ed). Meta-Research; Methods and Protocols. New York: Humana; 2022. S. 91-102.

632. Schulz KF, Altman DG, Moher D et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c332. https://dx.doi.org/10.1136/bmj.c332.

633. Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. Lancet 2002; 359(9308): 781-785. https://dx.doi.org/10.1016/S0140-6736(02)07882-0.

634. Schünemann H, Brożek J, Guyatt G et al. GRADE handbook [online]. 2013 [Accessed: 27.05.2021]. URL: https://gdt.gradepro.org/app/handbook/handbook.html.

635. Schünemann HJ, Akl EA, Guyatt GH. Interpreting the results of patient reported outcome measures in clinical trials: the clinician's perspective. Health Qual Life Outcomes 2006; 4: 62. https://dx.doi.org/10.1186/1477-7525-4-62.

636. Schünemann HJ, Best D, Vist G et al. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. CMAJ 2003; 169(7): 677-680.

637. Schünemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 9. Grading evidence and recommendations. Health Res Policy Syst 2006; 4: 21. https://dx.doi.org/10.1186/1478-4505-4-21.

638. Schwarzer R, Rochau U, Saverno K et al. Systematic overview of cost-effectiveness thresholds in ten countries across four continents. J Comp Eff Res 2015; 4(5): 485-504. https://dx.doi.org/10.2217/cer.15.38.

639. Sculpher M. The role and estimation of productivity costs in economic evaluation. In: Drummond MF, McGuire A (Ed). Economic evaluation in health care; merging theorey with practice. Oxford: Oxford University Press; 2001. S. 94-112.

640. Sculpher MJ, O'Brien BJ. Income effects of reduced health and health effects of reduced income: implications for health-state valuation. Med Decis Making 2000; 20(2): 207-215. https://dx.doi.org/10.1177/0272989X0002000206.

641. Senn S. Inherent difficulties with active control equivalence studies. Stat Med 1993; 12(24): 2367-2375. https://dx.doi.org/10.1002/sim.4780122412.

642. Senn S. The many modes of meta. Drug Inf J 2000; 34(2): 535-549. https://dx.doi.org/10.1177/009286150003400222.

643. Senn S. Cross-over trials in clinical research. Chichester: Wiley; 2002.

644. Senn S. Trying to be precise about vagueness. Stat Med 2007; 26(7): 1417-1430. https://dx.doi.org/10.1002/sim.2639.

645. Shamseer L, Moher D, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 350: g7647. https://dx.doi.org/10.1136/bmj.g7647.

646. Shea BJ, Bouter LM, Peterson J et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One 2007; 2(12): e1350. https://dx.doi.org/10.1371/journal.pone.0001350.

647. Shea BJ, Grimshaw JM, Wells GA et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007; 7: 10. https://dx.doi.org/10.1186/1471-2288-7-10.

648. Shea BJ, Hamel C, Wells GA et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009; 62(10): 1013-1020. https://dx.doi.org/10.1016/j.jclinepi.2008.10.009.

649. Shea BJ, Reeves BC, Wells G et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017; 358: j4008. https://dx.doi.org/10.1136/bmj.j4008.

650. Shechter SM, Schaefer AJ, Braithwaite RS et al. Increasing the efficiency of Monte Carlo cohort simulations with variance reduction techniques. Med Decis Making 2006; 26(5): 550-553. https://dx.doi.org/10.1177/0272989X06290489.

651. Shekelle PG, Ortiz E, Rhodes S et al. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? JAMA 2001; 286(12): 1461-1467. https://dx.doi.org/10.1001/jama.286.12.1461.

652. Shojania KG, Sampson M, Ansari MT et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007; 147(4): 224-233. https://dx.doi.org/10.7326/0003-4819-147-4-200708210-00179.

653. Siebert U. When should decision-analytic modeling be used in the economic evaluation of health care? Eur J Health Econ 2003; 4(3): 143-150. https://dx.doi.org/10.1007/s10198-003-0205-2.

654. Siebert U. Entscheidungsanalytische Modelle zur Sicherung der Übertragbarkeit internationaler Evidenz von HTA auf den Kontext des deutschen Gesundheitssystems: Ein Methodenbeitrag zu HTA [online]. 2005 [Accessed: 01.02.2021]. URL: https://portal.dimdi.de/de/hta/hta_berichte/hta099_bericht_de.pdf.

655. Siering U, Eikermann M, Hausner E et al. Appraisal tools for clinical practice guidelines: a systematic review. PLoS One 2013; 8(12): e82915. https://dx.doi.org/10.1371/journal.pone.0082915.

656. Signorovitch JE, Wu EQ, Yu AP et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics 2010; 28(10): 935-945. https://dx.doi.org/10.2165/11538370-000000000-00000.

657. Silvestre MA, Dans LF, Dans AL. Trade-off between benefit and harm is crucial in health screening recommendations. Part II: evidence summaries. J Clin Epidemiol 2011; 64(3): 240-249. https://dx.doi.org/10.1016/j.jclinepi.2010.09.008.

658. Simmonds MC, Higgins JP. Covariate heterogeneity in meta-analysis: criteria for deciding between meta-regression and individual patient data. Stat Med 2007; 26(15): 2982-2999. https://dx.doi.org/10.1002/sim.2768.

659. Simmonds MC, Higgins JP. A general framework for the use of logistic regression models in meta-analysis. Stat Methods Med Res 2016; 25(6): 2858-2877. https://dx.doi.org/10.1177/0962280214534409.

660. Simon R, Altman DG. Statistical aspects of prognostic factor studies in oncology. Br J Cancer 1994; 69(6): 979-985. https://dx.doi.org/10.1038/bjc.1994.192.

661. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst 2009; 101(21): 1446-1452. https://dx.doi.org/10.1093/jnci/djp335.

662. Siontis KC, Siontis GC, Contopoulos-Ioannidis DG et al. Diagnostic tests often fail to lead to changes in patient outcomes. J Clin Epidemiol 2014; 67(6): 612-621. https://dx.doi.org/10.1016/j.jclinepi.2013.12.008.

663. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

664. Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses--sometimes informative, usually misleading. BMJ 1999; 318(7197): 1548-1551. https://dx.doi.org/10.1136/bmj.318.7197.1548.

665. Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. Stat Med 1995; 14(24): 2685-2699. https://dx.doi.org/10.1002/sim.4780142408.

666. Söletormos G, Duffy MJ, Hayes DF et al. Design of tumor biomarker-monitoring trials: a proposal by the European Group on Tumor Markers. Clin Chem 2013; 59(1): 52-59. https://dx.doi.org/10.1373/clinchem.2011.180778.

667. Song F, Loke YK, Walsh T et al. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ 2009; 338: b1147. https://dx.doi.org/10.1136/bmj.b1147.

668. Song F, Parekh S, Hooper L et al. Dissemination and publication of research findings: an updated review of related biases. Health Technol Assess 2010; 14(8): iii, ix-xi, 1-193. https://dx.doi.org/10.3310/hta14080.

669. Spencer FA, Iorio A, You J et al. Uncertainties in baseline risk estimates and confidence in treatment effects. BMJ 2012; 345: e7401. https://dx.doi.org/10.1136/bmj.e7401.

670. Spiegelhalter DJ, Freedman LS, Parmar MKB. Bayesian Approaches to Randomized Trials. J R Stat Soc Ser A Stat Soc 1994; 157(3): 357-387. https://dx.doi.org/10.2307/2983527.

671. Spiegelhalter DJ, Myles JP, Jones DR et al. Methods in health service research. An introduction to bayesian methods in health technology assessment. BMJ 1999; 319(7208): 508-512. https://dx.doi.org/10.1136/bmj.319.7208.508.

672. St-Pierre C, Desmeules F, Dionne CE et al. Psychometric properties of self-reported questionnaires for the evaluation of symptoms and functional limitations in individuals with rotator cuff disorders: a systematic review. Disabil Rehabil 2016; 38(2): 103-122. https://dx.doi.org/10.3109/09638288.2015.1027004.

673. Stansfield C, O'Mara-Eves A, Thomas J. Text mining for search term development in systematic reviewing: A discussion of some methods and challenges. Res Synth Methods 2017; 8(3): 355-365. https://dx.doi.org/10.1002/jrsm.1250.

674. Statens Beredning för Medicinsk och Social Utvärdering. Utvärdering av metoder i hälso- och sjukvården och insatser i socialtjänsten [online]. 2017 [Accessed: 10.08.2021]. URL: http://www.sbu.se/globalassets/ebm/metodbok/sbushandbok.pdf.

675. Statistisches Bundesamt. Verbraucherpreisindizes [online]. [Accessed: 01.02.2021]. URL: https://www.destatis.de/DE/Themen/Wirtschaft/Preise/Verbraucherpreisindex/Publikationen/_publikationen-verbraucherpreisindex.html.

676. Steiner JF. The use of stories in clinical research and health policy. JAMA 2005; 294(22): 2901-2904. https://dx.doi.org/10.1001/jama.294.22.2901.

677. Steinhauser S, Schumacher M, Rücker G. Modelling multiple thresholds in meta-analysis of diagnostic test accuracy studies. BMC Med Res Methodol 2016; 16(1): 97. https://dx.doi.org/10.1186/s12874-016-0196-1.

678. Sterne JA, Hernan MA, Reeves BC et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355: i4919. https://dx.doi.org/10.1136/bmj.i4919.

679. Sterne JAC, Savovic J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898. https://dx.doi.org/10.1136/bmj.l4898.

680. Stewart LA, Clarke M, Rovers M et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015; 313(16): 1657-1665. https://dx.doi.org/10.1001/jama.2015.3656.

681. Steyerberg EW, Moons KG, van der Windt DA et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. PLoS Med 2013; 10(2): e1001381. https://dx.doi.org/10.1371/journal.pmed.1001381.

682. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998; 18(2 Suppl): S68-80. https://dx.doi.org/10.1177/0272989X98018002S09.

683. Stollenwerk B, Lhachimi SK, Briggs A et al. Communicating the parameter uncertainty in the IQWiG efficiency frontier to decision-makers. Health Econ 2015; 24(4): 481-490. https://dx.doi.org/10.1002/hec.3041.

684. Sturtz S, Bender R. Unsolved issues of mixed treatment comparison meta-analysis: network size and inconsistency. Res Synth Methods 2012; 3(4): 300-311. https://dx.doi.org/10.1002/jrsm.1057.

685. Suarez-Almazor ME, Belseck E, Homik J et al. Identifying clinical trials in the medical literature with electronic databases: MEDLINE alone is not enough. Control Clin Trials 2000; 21(5): 476-487. https://dx.doi.org/10.1016/s0197-2456(00)00067-2.

686. Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. J Clin Epidemiol 1996; 49(8): 907-916. https://dx.doi.org/10.1016/0895-4356(96)00025-X.

687. Sun X, Briel M, Walter SD et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010; 340: c117. https://dx.doi.org/10.1136/bmj.c117.

688. Sutton A, Ades AE, Cooper N et al. Use of indirect and mixed treatment comparisons for technology assessment. Pharmacoeconomics 2008; 26(9): 753-767. https://dx.doi.org/10.2165/00019053-200826090-00006.

689. Swart E, Bitzer EM, Gothe H et al. STandardisierte BerichtsROutine für Sekundärdaten Analysen (STROSA) – ein konsentierter Berichtsstandard für Deutschland, Version 2. Gesundheitswesen 2016; 78(S 01): e145-e160. https://dx.doi.org/10.1055/s-0042-108647.

690. Swart E, Ihle P, Gothe H et al. Routinedaten im Gesundheitswesen; Handbuch Sekundärdatenanalyse; Grundlagen, Methoden und Perspektiven. Bern: Huber; 2014.

691. Swift TL, Dieppe PA. Using expert patients' narratives as an educational resource. Patient Educ Couns 2005; 57(1): 115-121. https://dx.doi.org/10.1016/j.pec.2004.05.004.

692. Tai FM, Willson ML, Ghersi D. Implications of searching multiple trial registries: how should we search ClinicalTrials.gov and WHO ICTRP? [online]. 2012 [Accessed: 01.02.2021]. URL: https://abstracts.cochrane.org/2012-auckland/implications-searching-multiple-trial-registries-how-should-we-search.

693. Taichman DB, Sahni P, Pinborg A et al. Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors. PLoS Med 2017; 14(6): e1002315. https://dx.doi.org/10.1371/journal.pmed.1002315.

694. Tainio M, Tuomisto JT, Hänninen O et al. Parameter and model uncertainty in a life-table model for fine particles (PM2.5): a statistical modeling study. Environ Health 2007; 6: 24. https://dx.doi.org/10.1186/1476-069X-6-24.

695. Tajik P, Zwinderman AH, Mol BW et al. Trial designs for personalizing cancer care: a systematic review and classification. Clin Cancer Res 2013; 19(17): 4578-4588. https://dx.doi.org/10.1158/1078-0432.CCR-12-3722.

696. Takwoingi Y, Guo B, Riley RD et al. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. Stat Methods Med Res 2017; 26(4): 1896-1911. https://dx.doi.org/10.1177/0962280215592269.

697. Takwoingi Y, Leeflang MM, Deeks JJ. Empirical evidence of the importance of comparative studies of diagnostic test accuracy. Ann Intern Med 2013; 158(7): 544-554. https://dx.doi.org/10.7326/0003-4819-158-7-201304020-00006.

698. Tan SS. Microcosting in Economic Evaluations; Issues of accuracy, feasibility, consistency and generalisability [online]. 2009 [Accessed: 01.02.2021]. URL: http://repub.eur.nl/res/pub/17354/091127_Tan,%20Siok%20Swan.pdf.

699. Tan SS, Bouwmans CA, Rutten FF et al. Update of the Dutch Manual for Costing in Economic Evaluations. Int J Technol Assess Health Care 2012; 28(2): 152-158. https://dx.doi.org/10.1017/S0266462312000062.

700. Thomas J, Harden A, Oakley A et al. Integrating qualitative research with trials in systematic reviews. BMJ 2004; 328(7446): 1010-1012. https://dx.doi.org/10.1136/bmj.328.7446.1010.

701. Thomas S. Klinische Relevanz von Therapieeffekten: systematische Sichtung, Klassifizierung und Bewertung methodischer Konzepte. Duisburg/Essen: Universität; 2009.

702. Thompson JC, Quigley JM, Halfpenny NJ et al. Importance and methods of searching for E-publications ahead of print in systematic reviews. Evid Based Med 2016; 21(2): 55-59. https://dx.doi.org/10.1136/ebmed-2015-110374.

703. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002; 21(11): 1559-1573. https://dx.doi.org/10.1002/sim.1187.

704. Thorlund K, Devereaux PJ, Wetterslev J et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol 2009; 38(1): 276-286. https://dx.doi.org/10.1093/ije/dyn179.

705. Thurow S. Search engine visibility. Berkley: New Riders; 2008.

706. Tian L, Cai T, Pfeffer MA et al. Exact and efficient inference procedure for meta-analysis and its application to the analysis of independent 2 x 2 tables with all available data but without artificial continuity correction. Biostatistics 2009; 10(2): 275-281. https://dx.doi.org/10.1093/biostatistics/kxn034.

707. Tierney JF, Stewart LA, Ghersi D et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16. https://dx.doi.org/10.1186/1745-6215-8-16.

708. Torgerson DJ. Contamination in trials: is cluster randomisation the answer? BMJ 2001; 322: 355. https://dx.doi.org/10.1136/bmj.322.7282.355.

709. Torrance GW, Siegel JE, Luce BR et al. Framing and designing the cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB et al (Ed). Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996. S. 54-81.

710. Trevena LJ, Davey HM, Barratt A et al. A systematic review on communicating with patients about evidence. J Eval Clin Pract 2006; 12(1): 13-23. https://dx.doi.org/10.1111/j.1365-2753.2005.00596.x.

711. Tricco AC, Langlois EV, Straus SE. Rapid reviews to strengthen health policy and systems: a practical guide [online]. 2017 [Accessed: 05.02.2021]. URL: https://apps.who.int/iris/bitstream/handle/10665/258698/9789241512763-eng.pdf.

712. Trueman P, Drummond M, Hutton J. Developing guidance for budget impact analysis. Pharmacoeconomics 2001; 19(6): 609-621. https://dx.doi.org/10.2165/00019053-200119060-00001.

713. Tukey JW. Some thoughts on clinical trials, especially problems of multiplicity. Science 1977; 198(4318): 679-684. https://dx.doi.org/10.1126/science.333584.

714. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003; 290(12): 1624-1632. https://dx.doi.org/10.1001/jama.290.12.1624.

715. Turner RM, Omar RZ, Yang M et al. A multilevel model framework for meta-analysis of clinical trials with binary outcomes. Stat Med 2000; 19(24): 3417-3432. https://dx.doi.org/10.1002/1097-0258(20001230)19:24<3417::aid-sim614>3.0.co;2-l.

716. U.S. Food and Drug Administration. Devices@FDA [online]. [Accessed: 01.02.2021]. URL: http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm.

717. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs [online]. [Accessed: 01.02.2021]. URL: https://www.accessdata.fda.gov/scripts/cder/daf/.

718. U.S. Food and Drug Administration. Guidance for Industry; Developing Medical Imaging Drug and Biological Products; Part 2: Clinical Indications [online]. 2004 [Accessed: 01.02.2021]. URL: https://www.fda.gov/media/71226/download.

719. U.S. Food and Drug Administration. Guidance for Industry; Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims [online]. 2009 [Accessed: 01.02.2021]. URL: https://www.fda.gov/media/77832/download.

720. Unkel S, Amiri M, Benda N et al. On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assessment of therapies. Pharm Stat 2019; 18(2): 166-183. https://dx.doi.org/10.1002/pst.1915.

721. van Aert RCM, Wicherts JM, van Assen M. Publication bias examined in meta-analyses from psychology and medicine: A meta-meta-analysis. PLoS One 2019; 14(4): e0215052. https://dx.doi.org/10.1371/journal.pone.0215052.

722. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002; 21(4): 589-624. https://dx.doi.org/10.1002/sim.1040.

723. Van Tinteren H, Hoekstra OS, Boers M. Do we need randomised trials to evaluate diagnostic procedures? For. Eur J Nucl Med Mol Imaging 2004; 31(1): 129-131. https://dx.doi.org/10.1007/s00259-003-1384-x.

724. van Tinteren H, Hoekstra OS, Smit EF et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. Lancet 2002; 359(9315): 1388-1393. https://dx.doi.org/10.1016/s0140-6736(02)08352-6.

725. van Tulder M, Furlan A, Bombardier C et al. Updated Method Guidelines for Systematic Reviews in the Cochrane Collaboration Back Review Group. Spine (Phila Pa 1976) 2003; 28(12): 1290-1299. https://dx.doi.org/10.1097/01.BRS.0000065484.95996.AF.

726. Vandenbroucke JP, von Elm E, Altman DG et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007; 147(8): W163-194. https://dx.doi.org/10.7326/0003-4819-147-8-200710160-00010-w1.

727. Veerman JL, Mackenbach JP, Barendregt JJ. Validity of predictions in health impact assessment. J Epidemiol Community Health 2007; 61(4): 362-366. https://dx.doi.org/10.1136/jech.2006.047480.

728. Veroniki AA, Jackson D, Bender R et al. Methods to calculate uncertainty in the estimated overall effect size from a random-effects meta-analysis. Res Synth Methods 2019; 10(1): 23-43. https://dx.doi.org/10.1002/jrsm.1319.

729. Veroniki AA, Jackson D, Viechtbauer W et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods 2016; 7(1): 55-79. https://dx.doi.org/10.1002/jrsm.1164.

730. Veroniki AA, Jackson D, Viechtbauer W et al. Recommendations for quantifying the uncertainty in the summary intervention effect and estimating the between-study heterogeneity variance in random-effects meta-analysis. Cochrane Database Syst Rev 2015; (Suppl 1: Cochrane Methods): 25-27. https://dx.doi.org/10.1002/14651858.CD201501.

731. Vidanapathirana J, Abramson MJ, Forbes A et al. Mass media interventions for promoting HIV testing. Cochrane Database Syst Rev 2005; (3): CD004775. https://dx.doi.org/10.1002/14651858.CD004775.pub2.

732. Vijan S. Should we abandon QALYs as a resource allocation tool? Pharmacoeconomics 2006; 24(10): 953-954. https://dx.doi.org/10.2165/00019053-200624100-00003.

733. Villar J, Mackey ME, Carroli G et al. Meta-analyses in systematic reviews of randomized controlled trials in perinatal medicine: comparison of fixed and random effects models. Stat Med 2001; 20(23): 3635-3647. https://dx.doi.org/10.1002/sim.1096.

734. Virtanen H, Leino-Kilpi H, Salantera S. Empowering discourse in patient education. Patient Educ Couns 2007; 66(2): 140-146. https://dx.doi.org/10.1016/j.pec.2006.12.010.

735. Viswanathan M, Ansari MT, Berkman ND et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews [online]. 2012 [Accessed: 01.02.2021]. URL: https://www.ncbi.nlm.nih.gov/books/NBK91433/pdf/Bookshelf_NBK91433.pdf.

736. Vlayen J, Aertgeerts B, Hannes K et al. A systematic review of appraisal tools for clinical practice guidelines: multiple similarities and one common deficit. Int J Qual Health Care 2005; 17(3): 235-242. https://dx.doi.org/10.1093/intqhc/mzi027.

737. von Elm E, Altman DG, Egger M et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007; 335(7624): 806-808. https://dx.doi.org/10.1136/bmj.39335.541782.AD.

738. Waffenschmidt S, Janzen T, Hausner E et al. Simple search techniques in PubMed are potentially suitable for evaluating the completeness of systematic reviews. J Clin Epidemiol 2013; 66(6): 660-665. https://dx.doi.org/10.1016/j.jclinepi.2012.11.011.

739. Waffenschmidt S, Navarro-Ruan T, Hobson N et al. Development and validation of study filters for identifying controlled non-randomized studies in PubMed and Ovid MEDLINE. Res Synth Methods 2020; 11(5): 617-626. https://dx.doi.org/10.1002/jrsm.1425.

740. Wallace BC, Noel-Storr A, Marshall IJ et al. Identifying reports of randomized controlled trials (RCTs) via a hybrid machine learning and crowdsourcing approach. J Am Med Inform Assoc 2017; 24(6): 1165-1168. https://dx.doi.org/10.1093/jamia/ocx053.

741. Walter U, Schwartz FW. Prävention. In: Schwartz FW, Badura B, Busse R et al (Ed). Das Public Health Buch; Gesundheit und Gesundheitswesen. München: Urban und Fischer; 2003. S. 189-214.

742. Weinstein MC, O'Brien B, Hornberger J et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value Health 2003; 6(1): 9-17. https://dx.doi.org/10.1046/j.1524-4733.2003.00234.x.

743. Weinstein MC, Siegel JE, Garber AM et al. Productivity costs, time costs and health-related quality of life: a response to the Erasmus Group. Health Econ 1997; 6(5): 505-510. https://dx.doi.org/10.1002/(sici)1099-1050(199709)6:5<505::aid-hec294>3.0.co;2-i.

744. Weir CJ, Walley RJ. Statistical evaluation of biomarkers as surrogate endpoints: a literature review. Stat Med 2006; 25(2): 183-203. https://dx.doi.org/10.1002/sim.2319.

745. West S, King V, Carey TS et al. Systems to Rate the Strength of Scientific Evidence; Summary [online]. 2002 [Accessed: 01.02.2021]. URL: https://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf.

746. Wetterslev J, Thorlund K, Brok J et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008; 61(1): 64-75. https://dx.doi.org/10.1016/j.jclinepi.2007.03.013.

747. Wetzel H. Mindestmengen zur Qualitätssicherung: Konzeptionelle und methodische Überlegungen zur Festlegung und Evaluation von Fallzahlgrenzwerten für die klinische Versorgung. Z Arztl Fortbild Qualitatssich 2006; 100(2): 99-106.

748. Whiting P, Rutjes AW, Reitsma JB et al. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. Ann Intern Med 2004; 140(3): 189-202. https://dx.doi.org/10.7326/0003-4819-140-3-200402030-00010.

749. Whiting P, Savovic J, Higgins JP et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 2016; 69: 225-234. https://dx.doi.org/10.1016/j.jclinepi.2015.06.005.

750. Whiting PF, Rutjes AW, Westwood ME et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155(8): 529-536. https://dx.doi.org/10.7326/0003-4819-155-8-201110180-00009.

751. Whiting PF, Rutjes AW, Westwood ME et al. A systematic review classifies sources of bias and variation in diagnostic test accuracy studies. J Clin Epidemiol 2013; 66(10): 1093-1104. https://dx.doi.org/10.1016/j.jclinepi.2013.05.014.

752. Whitlock EP, Lin JS, Chou R et al. Using existing systematic reviews in complex systematic reviews. Ann Intern Med 2008; 148(10): 776-782. https://dx.doi.org/10.7326/0003-4819-148-10-200805200-00010.

753. Widrig D, Tag B. HTA and its legal issues: a framework for identifying legal issues in health technology assessment. Int J Technol Assess Health Care 2014; 30(6): 587-594. https://dx.doi.org/10.1017/S0266462314000683.

754. Wieseler B, Kerekes MF, Vervoelgyi V et al. Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports, and journal publications. BMJ 2012; 344: d8141. https://dx.doi.org/10.1136/bmj.d8141.

755. Wigge P. Evidenz-basierte Richtlinien und Leitlinien. Medizinrecht 2000; 18(12): 574-585. https://dx.doi.org/10.1007/s003500000381.

756. Wiksten A, Rücker G, Schwarzer G. Hartung-Knapp method is not always conservative compared with fixed-effect meta-analysis. Stat Med 2016; 35(15): 2503-2515. https://dx.doi.org/10.1002/sim.6879.

757. Windeler J. Bedeutung randomisierter klinischer Studien mit relevanten Endpunkten für die Nutzenbewertung. In: Begriffsdefinitionen und Einführung; Dokumentation des ersten gemeinsamen Workshops von GFR und IQWiG am 4. September 2007 in Berlin. Bonn: Gesundheitsforschungsrat des Bundesministeriums für Bildung und Forschung; 2007. S. 26-31.

758. Windeler J. Externe Validität. Z Evid Fortbild Qual Gesundhwes 2008; 102(4): 253-259. https://dx.doi.org/10.1016/j.zefq.2008.04.006.

759. Windeler J, Conradt C. Wie können "Signifikanz" und "Relevanz" verbunden werden? Med Klin (Munich) 1999; 94(11): 648-651. https://dx.doi.org/10.1007/BF03045008.

760. Windeler J, Lange S. Nutzenbewertung in besonderen Situationen – Seltene Erkrankungen. Z Evid Fortbild Qual Gesundhwes 2008; 102(1): 25-30. https://dx.doi.org/10.1016/j.zgesun.2007.12.005.

761. Windeler J, Ziegler S. Evidenzklassifizierungen. Z Arztl Fortbild Qualitatssich 2003; 97(6): 513-514.

762. Wolff RF, Moons KGM, Riley RD et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med 2019; 170(1): 51-58. https://dx.doi.org/10.7326/M18-1376.

763. Wong SS, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455.

764. Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc 2006; 94(1): 41-47.

765. Wong SS, Wilczynski NL, Haynes RB. Optimal CINAHL search strategies for identifying therapy studies and review articles. J Nurs Scholarsh 2006; 38(2): 194-199. https://dx.doi.org/10.1111/j.1547-5069.2006.00100.x.

766. Wood L, Egger M, Gluud LL et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ 2008; 336(7644): 601-605. https://dx.doi.org/10.1136/bmj.39465.451748.AD.

767. Yang F, Wittes J, Pitt B. Beware of on-treatment safety analyses. Clin Trials 2019; 16(1): 63-70. https://dx.doi.org/10.1177/1740774518812774.

768. Zarin DA, Tse T, Williams RJ et al. Trial Reporting in ClinicalTrials.gov - The Final Rule. N Engl J Med 2016; 375(20): 1998-2004. https://dx.doi.org/10.1056/NEJMsr1611785.

769. Ziebland S, McPherson A. Making sense of qualitative data analysis: an introduction with illustrations from DIPEx (personal experiences of health and illness). Med Educ 2006; 40(5): 405-414. https://dx.doi.org/10.1111/j.1365-2929.2006.02467.x.

770. Ziegler DK, Mosier MC, Buenaver M et al. How much information about adverse effects of medication do patients want from physicians? Arch Intern Med 2001; 161(5): 706-713. https://dx.doi.org/10.1001/archinte.161.5.706.

771. Zorzela L, Loke YK, Ioannidis JP et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016; 352: i157. https://dx.doi.org/10.1136/bmj.i157.

772. Zschorlich B, Knelangen M, Bastian H. Die Entwicklung von Gesundheitsinformationen unter Beteiligung von Bürgerinnen und Bürgern am Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Gesundheitswesen 2011; 73(7): 423-429. https://dx.doi.org/10.1055/s-0030-1261879.

773. Zwarenstein M, Treweek S, Gagnier JJ et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008; 337: a2390. https://dx.doi.org/10.1136/bmj.a2390.