IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Institute for Quality and Efficiency in Health Care

In a nutshell

Facts and figures from IQWiG

2018

FOCUS: INTERNATIONAL AFFAIRS

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in Health Care (IQWiG)
Im Mediapark 8
50670 Köln
GERMANY
Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: info@iqwig.de

Internet
iqwig.de
informedhealth.org
themencheck-medizin.iqwig.de

Editor
Dr. phil. Beatrice Wolter

Graphic design
Désirée Gensrich, dbgw

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Using synergies: International network activities

Four large international health technology assessment networks have been established since 1993.

EUnetHTA. The European Network for Health Technology Assessment (EUnetHTA) was established in 2006 with funding from the European Union (see page 10 ff). In 2009, the project continued with funding from the founding members. Since 2010, part of its funding has been provided by the health programme of the European Union (EU). EUnetHTA's aim is to establish the collaboration of HTA organizations within Europe. Besides the development of conjointly used HTA information, this also includes the exchange of ideas and the conjoint development of methods. The 81 EUnetHTA partners comprise national and regional HTA agencies as well as research organizations. In 2011, HTA collaboration was provided with a legal basis in European law. In addition, since the beginning of 2018, the EU's political institutions have been negotiating on harmonizing benefit assessments of medical interventions at a European level. As a result, the network could be transferred into a different legal form. A total of 26 countries are represented in EUnetHTA:

Austria • Belgium • Bulgaria • Croatia • Czech Republic • Denmark • Estonia • Finland • France • Germany • Greece • Hungary • Ireland • Italy • Latvia • Lithuania • Netherlands • Norway • Poland • Portugal • Romania • Slovakia • Slovenia • Spain • Sweden • United Kingdom

HTAsiaLink. HTA agencies are relatively new in Asia. In 2006, as the first country in the region, Thailand introduced HTA in the form of the Health Intervention and Technology Assessment Program (HITAP). The HTA departments in the Taiwanese Center for Drug Evaluation (CDE) and the South-Korean National Evidence-based Health Collaborating Agency (NECA) were subsequently established in 2008. In 2011, these agencies established HTAsiaLink during an international symposium on the Asian version of the quality-adjusted life year (QALY). The network's aim is to promote research in the area of HTA by exchanging information and developing HTA methods for the Asian region. Today, HTAsiaLink has 14 members from 11 countries:

Australia • Bhutan • China • Malaysia • Philippines • Singapore • South Korea • Taiwan • Thailand • United Kingdom • Vietnam

RedETSA is the HTA network of Latin-American countries. It was established in 2011 in Rio de Janeiro as a non-profit network. The initiators were health ministries, regulatory authorities, HTA agencies, the World Health Organization, and various research organizations in the region. RedETSA currently has 30 members from 15 countries. Its aim is to promote HTA capacities in Latin-American countries, facilitate the exchange of information, as well as to support decisions on the reimbursement and use of medical technologies. The members have committed themselves to sharing their HTA products with other members via the RedETSA database. The network's Executive Committee is responsible for ensuring regular funding and for off-budget funding.

The RedETSA members are from:

Argentina • Bolivia • Brazil • Canada • Chile • Columbia • Costa Rica • Cuba • Ecuador • El Salvador • Mexico • Panama • Paraguay • Peru • Uruguay

INAHTA, the International Network of Agencies for Health Technology Assessment, is a non-profit organization that has its roots in the international HTA movement. The network was established in 1993 and currently comprises 50 agencies whose sphere of influence covers more than a billion people in 31 countries. All members are publicly funded. The network's aim is to exchange information on the production and dissemination of HTA reports. The INAHTA members are from:

Argentina • Australia • Austria • Belgium • Brazil • Canada • China • Columbia • Denmark • Finland • France • Germany • Ireland • Italy • Kazakhstan • Luxemburg • Malaysia • Mexico • Netherlands • Norway • Poland • Singapore • South Africa • South Korea • Spain • Sweden • Switzerland • Tunisia • United Kingdom • Uruguay • USA

WEB TIPS

eunethta.eu
htasialink.org
inahta.org
redetsa.org

Health economic evaluations: Experiences from seven countries

How strong is the impact of health economic evaluations on decisions in health care systems? What impact can they have on the provision of health care in a country?

Table updated. In 2014, a series of articles on health economic evaluations (HEEs) in seven countries was published in the German Journal of Evidence and Quality in Health Care (ZEFQ). Seven author teams provided contributions. IQWiG coordinated the project and wrote the German contribution, including a table providing an overview of the relevance and handling of HEEs in the seven countries. An updated version of this table from October 2018 is shown on pages 4 to 7.

How do other countries do it? Health economic evaluations in seven countries

	England	Sweden	Germany
Type of health care system	Beveridge system (tax funded)	Beveridge system (tax funded)	Bismarck system (contribution funded)
HTA agencies	NICE NSC, JCVI, HPA (since 2013, part of Public Health England, PHE)	TLV SBU, SALAR, NLT, NBHW, Public Health Agency of Sweden	IQWiG G-BA
HTA agency established in	NICE: 1999	TLV: 2002 SBU: 1987	IQWiG: 2004
HEE as official criterion	1999	2002	2007

Selection criteria. Why were and are these seven countries interesting? Countries with long experience and tradition (Australia) or strong internationally renowned research (England, the Netherlands) in HEEs were included. Their health insurance systems are either premium- or contribution-funded Bismarck systems (the Netherlands, Germany) or tax-funded Beveridge systems (England, Australia, Sweden). Sweden is also known for a long-standing debate on the prioritization of health care services. Finally, emerging countries are relevant that are at the same time working towards making health insurance systems accessible to broad population strata and are confronted with high health expenditure (Brazil, Thailand).

Short conclusion: HEEs have become indispensable internationally, in particular in the area of pharmaceuticals, where they create transparency for all stakeholders in the health care system. Their results are never translated directly on a one-to-one basis into reimbursement decisions, but are largely implemented after consideration of further criteria such as disease severity or ethical aspects.

LITERATURE TIP

The series of articles has been published in the German Journal of Evidence and Quality in Health Care: ZEFQ 2014; 108: 355-412.

	Australia	Netherlands	Brazil	Thailand
	Beveridge system (tax funded)	Bismarck system (premium funded)	Tax funded	3 public health insurance systems, Universal Health Coverage (UHC)
	PBAC MSAC, PLAC	ZINL (up to 2014: CVZ)	CONITEC	HITAP
	PBAC: 1953	CVZ: 1999	2011	2007
	1993	2005	2003	2004 / 2008

	England	Sweden	Germany
HEE conducted by	Manufacturer/external academic units	Manufacturer	Manufacturer and IQWiG
HEE scope	Mainly drugs, vaccines, public health	Drugs, medical devices, clinical guidelines, but also more general health care areas	Mainly drugs
HEE guidance (time of last update)	2013 and 2014	Guidance (TLV) 2017 and handbook (SBU) 2018	2017 as part of IQWiG's General Methods
HEE implementation for drugs	Negative list	Positive list	Negative list
HEE perspective	Health care system or societal	Societal	Community of SHI members
HEE outcome measure	QALY	QALY	Indication-specific outcomes (and QALY)
HEE threshold	20-30.000 British pounds/QALY	No	No
HEE impact (perceived)	Well established	Drugs: clear and explicit role	No role
HEE impact (actual practice)	Minor*	HEE is one of 3 basic principles in decision-making, but the impact is difficult to estimate, as the regions have great freedom of decision-making	Last measure in the AMNOG procedure if the arbitrary board fails to reach agreement; currently not relevant

* *As drugs are sometimes reimbursed as end-of-life drugs from special funds (e.g. cancer drugs from the Cancer Fund), some researchers view the actual effect of HEE results on reimbursement decisions for drugs to be minor. In addition, the impact of HEE results on price negotiations cannot be estimated, as these negotiations are confidential.*

	Australia	Netherlands	Brazil	Thailand
	Manufacturer	Manufacturer	Manufacturer	Health Economic Working Group and university/ private research with funding from public health insurance (approx. 12 to 18 reports per year)
	Mainly drugs, also medical devices, screening programmes, public health	Mainly drugs, but also medical devices	Mainly drugs, but also medical devices and other procedures	Drug benefits package for UHC, but also medical devices, vaccines, public health interventions
	2016	2016	2014	2014
	Positive list	Positive list	Positive list	Optimum list of drugs as a positive list (different to the WHO minimum list)
	Societal and health care system	Societal	Societal	Societal
	Mainly QALY	QALY	Indication-specific outcomes and QALY	Societal QALY
	No	No	No	160.000 baht (approx. 4300 euros) / QALY
	Drugs: clear and explicit role	Established	Established	Established for drugs
	Drugs: HEE as a "fourth hurdle" before inclusion in positive list	Minor; HEE as 1 of 4 recommendation criteria of ZIN (necessity, effectiveness, cost-effectiveness, and feasibility)	Rejection of reimbursement not alone due to HEE	Rejection of reimbursement due to HEE (exceptions possible)

▶ Abbreviations are defined on page 33

Internationally involved and in demand

Each year IQWiG receives numerous requests from abroad, mostly from international research representatives.

Worldwide activities. IQWiG's international involvement has been specified in the law since 2015 (Social Code Book V, §139a). The legislator thus converted the Institute's previous necessary collaboration in the international field of evidence-based medicine into a legal remit. A separate unit at IQWiG coordinates and maintains the Institute's worldwide contacts and activities. These include

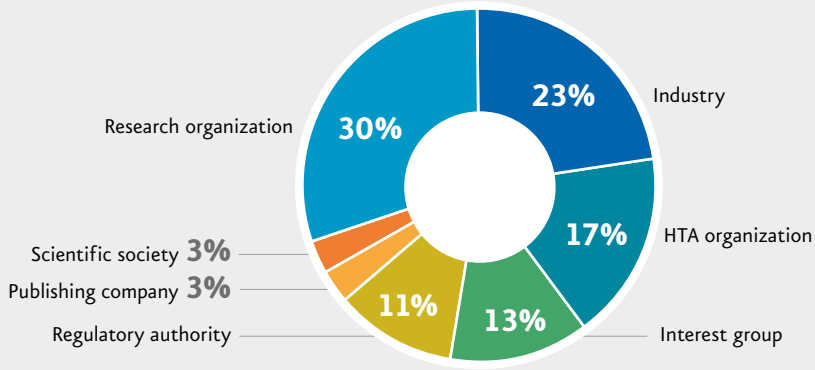
- involvement in international projects on evidence-based medicine
- comments on health technology assessment (HTA) methods at an international level
- participation in the European collaboration network EUnetHTA (see page 10ff)
- organization of the annual meeting of the international scientific society HTAi in Cologne in 2019 (as the Chair of the International Scientific Programme Committee, IQWiG is responsible for the meeting's content)

International involvement: Where and in what function?

Scientific society	IQWiG's function
HTA Network of Europe	▪ Scientific expert for Germany
European Network for HTA (EUnetHTA)	▪ Member of the Executive Committee ▪ Lead Partner "Quality Management, Scientific Guidance and Tools" (Work Package 6)
Health Technology Assessment international (HTAi)	▪ Member of the Board ▪ Chair of the Scientific Programme Committee for the annual meeting in 2019 in Cologne ▪ Chair of the Scientific Development and Capacity Building Committee ▪ Member of the Global Policy Forum
International Network of Agencies for HTA (INAHTA)	▪ Member
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	▪ Member of the HTA Roundtable Europe

Source: IQWiG, status: 30 September 2018

Who has requests?



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- representation in several international scientific societies in different functions (see left table).

EUnetHTA. As a founding member, IQWiG has been involved in the European Network for Health Technology Assessment (EUnetHTA) since 2006. The network's aim is to support international and scientific-technical collaboration in HTA. Together with the Belgian EUnetHTA partner KCE (Belgian Health Care Knowledge Centre), IQWiG is currently responsible for Work Package 6 "Quality Management, Scientific Guidance and Tools" (see page 10f). A EUnetHTA team specifically established for this purpose coordinates IQWiG's activities surrounding this project.

Requests from abroad. Each year the Institute receives numerous requests from representatives of international organizations. These requests refer to various issues and include requests for appointments to exchange opinions, for IQWiG's involvement in HTA events such as meetings and panels, for interviews, as well as for IQWiG's participation in international surveys. Representatives from research organizations and commercial companies most commonly contact IQWiG, besides HTA organizations, regulatory authorities, scientific societies, publishing companies, and political interest groups (see graph above).

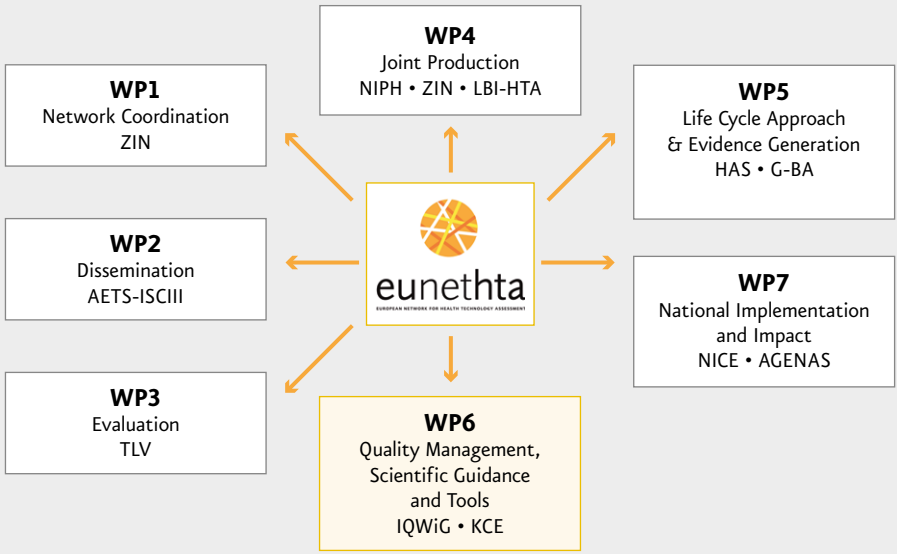
It's better in a network

EUnetHTA, the European network of HTA organizations, is faced with major challenges.

Network activities: Since 2006, the European Network for Health Technology Assessment (EUnetHTA) has been committed to promoting scientific and technical collaboration between European HTA agencies. This collaboration has been successful and the increasing number of members shows that network activities are in demand. In 2006, 15 partners were involved in the network – today there are more than 80.

Joint Action 3: With Joint Action 3 (JA3), EUnetHTA is currently in the fourth promotion phase of the European Health Programme, which runs from 2016 to 2020. Spread across

EUnetHTA Joint Action 3: 7 Work Packages (WP)



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these 4 years, funding of a volume of 20 million euros is available. JA3 is divided into 3 activity branches with 7 work packages.

In the first branch ("Implementation"), EUnetHTA products are generated in the work packages 1, 2, 4 and 5.
These include

- horizon scanning (monitoring of interventions with an expected high impact on the health care systems)
- joint and collaborative assessments (jointly generated assessments)
- early dialogues (consultations for manufacturers before the benefit assessment of drugs or medical devices)
- evidence generation after the marketing authorization of drugs (e.g. through data collection from registries)

Furthermore, these four work packages prepare recommendations on how consumers and patients, external experts and industry representatives can be involved in HTAs. In addition, the Work Package 1 teams provide scientific and technical support for the whole project.

In the second branch ("Quality Management and Methodology"), the Work Package 6 teams are creating a quality management system for EUnetHTA and also generating and revising methodological guidelines and tools (see page 12f).

In the third branch ("Analysis"), the Work Package 3 and 7 teams are monitoring whether the project goals are being achieved and assessing how successful the implementation of EUnetHTA products is in the national HTA contexts.

Future planning: What will happen after 2020? A proposal by the European Commission for a regulation on the assessment of health technologies has been available since January 2018. This proposal stipulates the binding use of jointly generated HTA reports and has been heavily criticized due to, among other things, extensive interference with the health care systems of the individual European member states. The legislative EU institutions are now negotiating about conditions under which a benefit assessment of drugs and medical devices can be implemented at the EU level. At the same time, it is the supreme goal of EUnetHTA Joint Action 3 to develop a sustainable model for HTA collaboration after 2020. The results are eagerly awaited, as ultimately the further funding of HTA collaboration at the European level is also at stake.

International collaboration: But how?

The European network EUnetHTA is developing a quality management system. The aim is to produce high-quality HTA reports throughout Europe.

Robust quality management required. If collaborative HTA work is supposed to function at the European level in the long term, then robust and sophisticated quality management (QM) is indispensable. Members of the EUnetHTA Work Package 6 led by IQWiG and the Belgian HTA organization KCE are designing this QM system and are working on its implementation (see page 10). The great importance of robust QM is also underlined by a proposal of the EU Commission on the promotion of HTA collaboration after 2020 (see page 11). EU committees have been discussing this, in part controversial, proposal since the beginning of 2018.

Components of the QM system (QMS)
These include:

- EUnetHTA quality policy
- processes and procedures
- organization

They are combined with QM measures such as

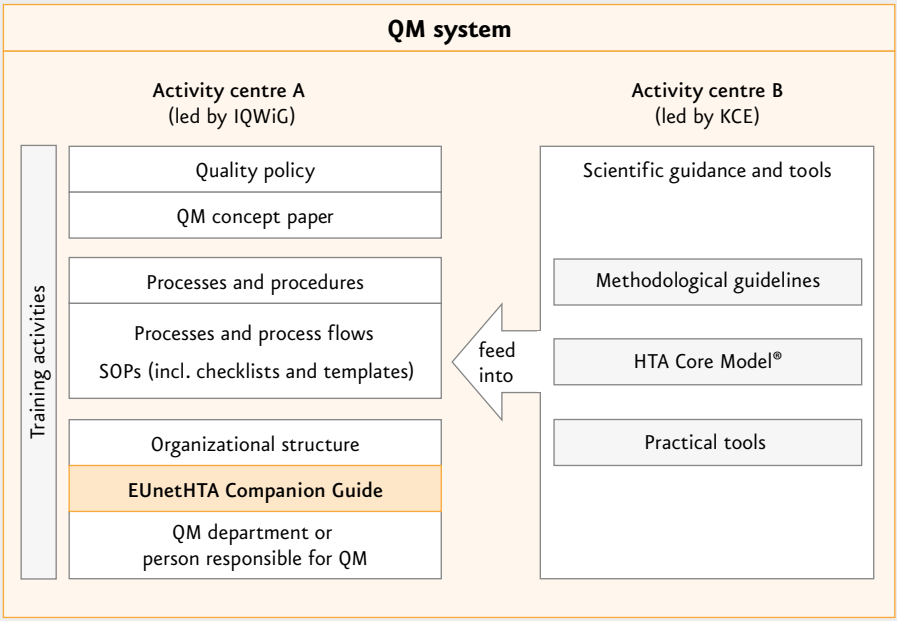
- planning
- assurance
- control
- improvement

The components and measures are to conjointly ensure the achievement of high quality reports. Processes, templates, methods and tools had already been generated in previous EUnetHTA working phases (e.g. Joint Action 2), which were followed by evaluations and internal workshops. On the basis of additional national expertise, the Joint Action 2 products were revised in Joint Action 3 and further products generated. The procedures are gradually being transferred into standard operating procedures (SOPs), which will then seamlessly and chronologically reflect the whole assessment process.

Improvement proposals desired. Checklists for quality control and useful templates supplement the SOPs with references to methodological guidelines and useful tools. The EUnetHTA Companion Guide provides support to the assessment teams during the production of the reports and enables easy access to the relevant instructions, i.e. it contains all SOPs, templates, guidelines and tools.

After completion of an assessment, the HTA producers have the option of submitting improvement proposals for all QMS components via a questionnaire, enabling continuous modification and improvement of the SOPs, templates, guidelines and tools.

EUnetHTA QM system: Summarized in the Companion Guide



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Up to date: IQWiG's scientific methods

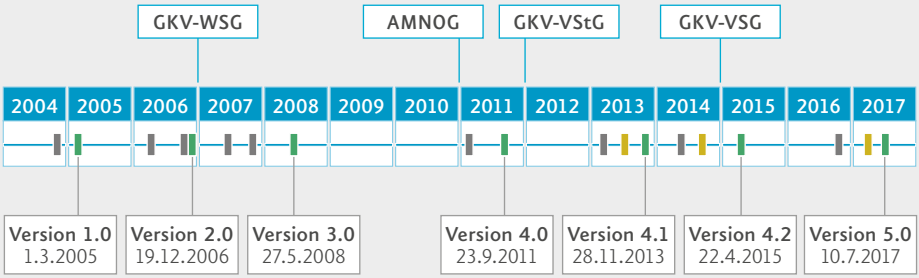
IQWiG's methods follow internationally accepted standards of evidence-based medicine.

Version 5.0. The Institute regularly updates its methods and adapts them to new legal requirements or international scientific developments. By now, Version 5.0 of the Institute's methods paper can be downloaded from iqwig.de. It contains detailed information on IQWiG's way of working, which is based on several key maxims:

Evidence-based, independent, transparent. IQWiG prepares its reports according to the principles of evidence-based medicine. This means that the results must always be reproducible and comprehensible. In addition, the Institute is independent in its scientific work. Neither industry nor health insurance funds nor authorities can influence the contents of its reports. Furthermore, anyone who is involved in the Institute's reports, whether internally or externally, must disclose all relationships that could influence the work and the results.

Patient-orientated. In the assessment of an examination or treatment method, the benefit for patients is the key criterion. Does the measure increase life expectancy, reduce symptoms or improve quality of life? To answer these questions, IQWiG regularly considers the patient perspective. The general public can also submit proposals for the assessment of examination and treatment methods in IQWiG's so-called "ThemenCheck Medizin". Finally, with its health information, the Institute objectively provides information on the state of medical knowledge (see page 18) to enable patients and other affected persons to make informed decisions.

Constantly updated: The IQWiG methods paper



GKV-WSG = GKV-Wettbewerbsstärkungsgesetz (SHI Act to Promote Competition)

AMNOG = Arzneimittelmarkt-Neuordnungsgesetz (Act on the Reform of the Market for Medicinal Products)

GKV-VStG = GKV-Versorgungsstrukturgesetz (SHI Health Care Structure Act)

GKV-VSG = GKV-Versorgungsstärkungsgesetz (SHI Act to Promote Health Care)

The first IQWiG methods paper (version 1.0) was published on 1 March 2005. Since then, the Institute has regularly revised its methods. The last version 5.0 of the General Methods was published in July 2017.

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Quality assured. All processes at IQWiG are targeted towards adherence to these principles. Various external and internal components have been implemented for quality assurance. For instance, as a standard, the Institute involves both external experts and patients to obtain external expertise and holds public hearings on preliminary versions of the reports. In addition, each document to be published undergoes a standard internal review to ensure the correctness and comprehensibility of the assessments (see page 16f).

International dimension. IQWiG's modular quality assurance system is the basis for the development of a standard process for the quality assurance of international HTA reports that is currently being developed at the level of the European network EUnetHTA (see page 12 f).

WEB TIP

The IQWiG methods paper version 5.0 is available on
iqwig.de > English version > Methods > Methods paper

Internal checks in two steps

Before publication, each document undergoes a two-step quality assurance process called QA1 and QA2.

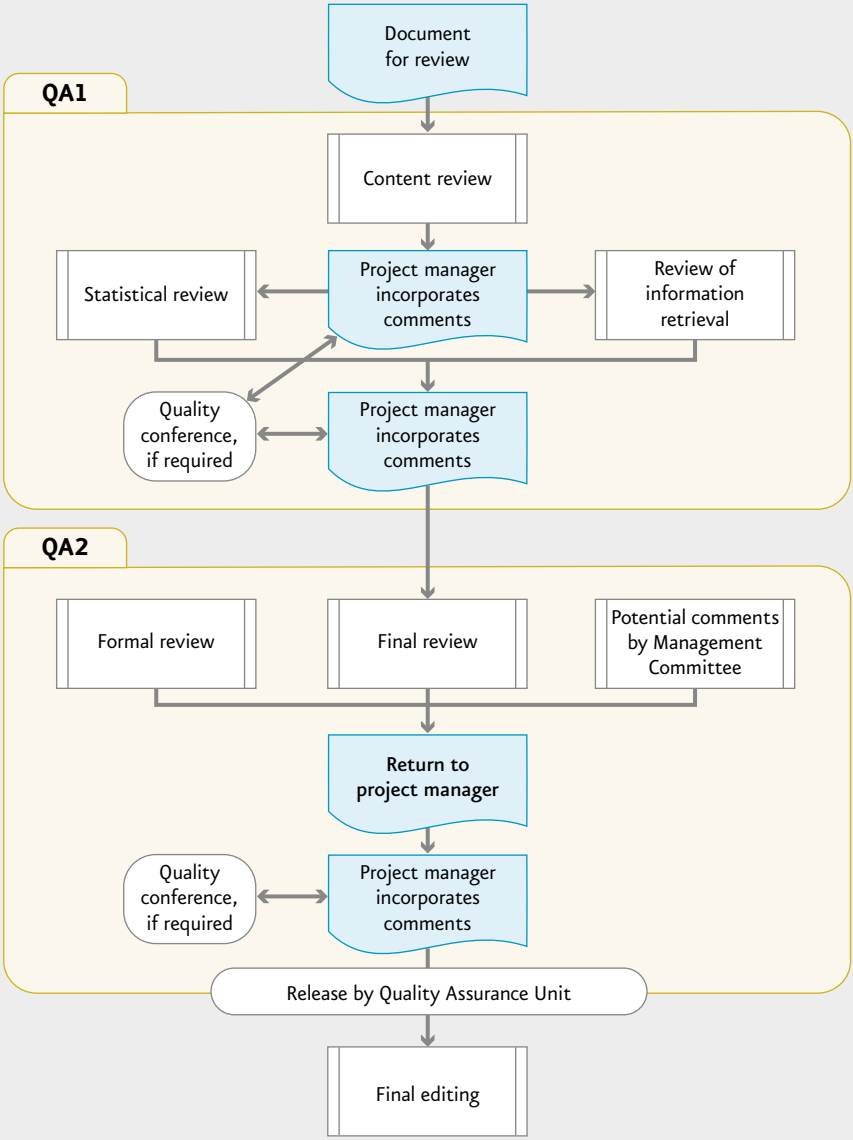
Step 1 (QA1): The mentor responsible for the project performs a detailed scientific review of the document of interest; this is completed by a statistical review and a review of information retrieval by colleagues in the corresponding scientific departments. The project manager incorporates all comments and generates a preliminary version of the document.

Step 2 (QA2): The project manager then submits the document consented by the project group for a formal-technical and a final content review. Independently of the previous course of the project, these two final reviews are performed by IQWiG researchers who do not belong to the project group. The Institute Management as well as IQWiG's supreme internal Management Committee may contribute comments in this phase.

All comments from the final review must be clarified before the Quality Assurance Unit releases a document for final editing, where it undergoes final formatting and is prepared for publication.

Aim: All review steps aim to ensure high-quality IQWiG documents. Templates for each report type help the project teams to work in a structured manner. This is because all IQWiG products must be correct not just with regard to methods, assessment standards and reporting, but must also be comprehensible for all target groups and consistent with one another. Only when this is the case is the final document sent to IQWiG's contracting agencies and then published.

Internal quality assurance: Two modules as a standard



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Informedhealth.org: The information portal for evidence-based medicine

Both patients and (healthy) consumers can find information on a wide range of different medical topics on this website.

Advantages and disadvantages. With the descriptive and easily understandable articles, illustrations and short films published on gesundheitsinformation.de and its English translation informedhealth.org, the Institute fulfils its legal remit to provide health information to the public. The website offers information on advantages and disadvantages of the main treatment options and health care services. This evidence-based information is intended to help users prepare their conversations with physicians or other medical professionals. It does not replace seeing a physician, however, and the website does not offer individual consultations.

Catalogue of topics. When selecting topics, the Institute uses various sources:

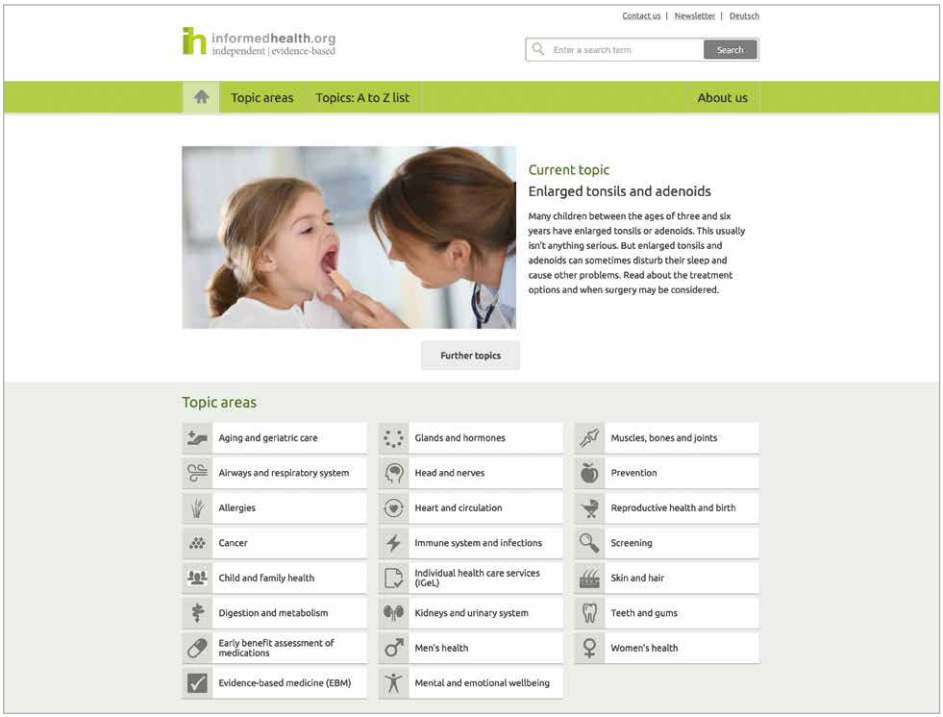
- The Institute mainly produces information on a catalogue of topics, particularly including common illnesses, diagnoses and health-related issues.
- The assessments and reports issued by the Institute are a further source of topics.
- In addition, the Federal Joint Committee or the Federal Ministry of Health may commission certain topics.

Furthermore, IQWiG also addresses topics suggested by members of the public.

Quality assurance. Draft versions of the articles undergo a multi-stage quality assurance process involving experts within and outside the Institute as well as patients. Before publication, the articles are also evaluated by users.

Up-to-dateness. The articles, illustrations and films on informedhealth.org are based on the best evidence available at the time of publication. The last update is shown at the bottom of each article. This is the date on which the information, and the underlying scientific evidence, were up-to-date. In order to ensure that the website is up-to-date, the Institute regularly checks and, if necessary, revises its content.

German and English. On 14 February 2006, the German-language website gesundheitsinformation.de went online. This was followed in May 2006 by the launch of the English-language version informedhealthonline.org, a one-to-one translation. The latter site was renamed "Informed Health" in November 2015, with the new address informedhealth.org. In 2018, the monthly average was about 800 000 visitors to gesundheitsinformation.de, and about 530 000 visitors to informedhealth.org.



Source: informedhealth.org [accessed on 24 January 2019]

Help with making medical decisions

Patients facing difficult decisions can use a list of questions published by the Institute on informedhealth.org as a decision aid.

Gaining clarity. The questions can help explore individual needs in the decision-making process, plan the next steps and track the progress. They also make it easier to share one's views with others who are involved in the decision. Building on one another, the questions comprise four steps:

1. What decision am I facing?
2. What are my options? Who can help me?
3. What do I need in order to be able to make a decision?
4. What else can I do to feel more confident about making a decision?

Preparing conversations. The decision aid cannot replace a professional consultation. But it can help prepare for a conversation with health care professionals or relatives.

Ottawa Personal Decision Guide (OPDG). The OPDG was developed by the Ottawa Hospital Research Institute in 2015 and is available as an interactive PDF on informedhealth.org. The German-language decision aid is based on the OPDG and is available on gesundheitsinformation.de. In addition, IQWiG has produced different formats of evidence-based information on nine medical conditions, providing information on the benefit and harm of medical and diagnostic procedures. These include:

- abdominal aortic aneurysms (screening)
- breast cancer (screening)
- colorectal cancer (screening)
- cervical cancer (screening)
- prostate cancer (screening)
- endometriosis (treatment)
- uterine fibroids (treatment)
- pelvic organ prolapse (treatment)
- heavy periods (treatment)

WEB TIPS

Information on the IQWiG decision aids:
informedhealth.org/decision-aid.2221.en.html

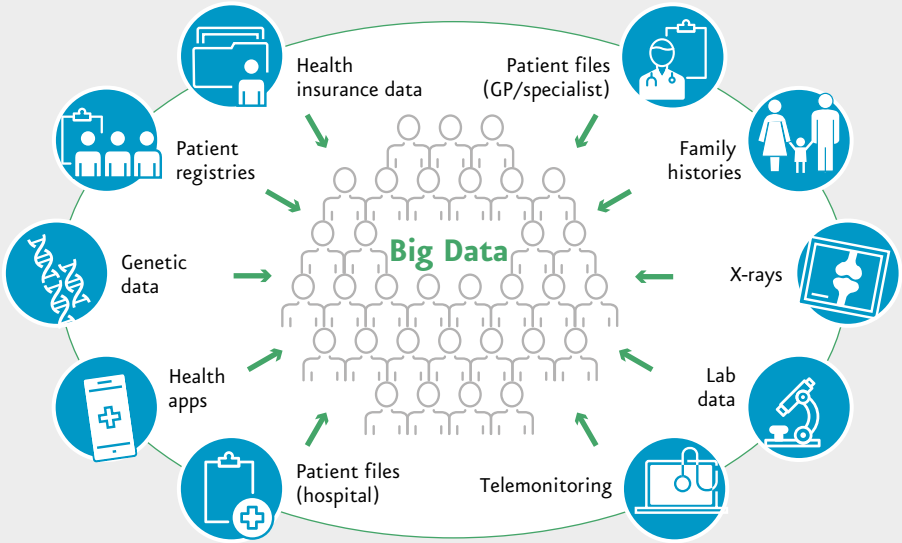
To the Ottawa Personal Decision Guide, produced by O'Connor, Stacey, Jacobsen, Ottawa Hospital Research Institute and University of Ottawa. Canada; 2015.
https://decisionaid.ohri.ca/docs/das/opdg.pdf

Big data in medicine: What is it all about?

"Big data" is a colourful term. Those believing in progress consider it a magic word with an all-embracing promise for solutions. Does it keep this promise?

Various levels of meaning. In the literal sense, the term "big data" means huge, diverse, and rapidly changing data pools that cannot be analysed with conventional digital processing techniques. At the same time, it is used as a catchword for the designation of new information technologies that are supposed to be capable of collecting, consolidating, saving and analysing information.

Sources for big data in health care – some examples



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Established applications. Big data analyses are already being used in modern weather forecasting, control of electricity grids or targeted marketing on the basis of customer data analyses.

And in medicine? Here, big data are supposed to support the generation of new knowledge, for instance, in benefit assessments of medical interventions. Apart from that, they are expected to enable progress in individual patient care. According to big data advocates, a prerequisite for such progress is far-reaching access of researchers and clinicians to the personal interlinked health data of as many patients as possible (see chart on the left).

Benefit assessment without causality? How does the big data methodology for the generation of new knowledge work? Simply put, programs with continuously optimized analysis algorithms trawl big data for relational patterns. The motto is: the more data, the better. These programs do not aim at investigating hypotheses on cause-effect relationships, as meticulous clinical studies do. The digital screening process is supposed to result in the provision of reliable results on the benefit of medical procedures under detailed consideration of individual patient characteristics. This is impossible from the perspective of evidence-based medicine, as a treatment's efficacy and benefit can only be proven by causality, not by correlation. The proof of causal relationships requires prospective and, ideally, randomized controlled trials. Nevertheless, many big data advocates are waiting to shake up the established understanding of science while making great promises, which in the field of medicine, however, are far from being fulfilled.

Is there a benefit for the individual patient? In one form of the clinical application of big data, the patient's data pattern is subjected to a similarity analysis in the knowledge base of a mainframe computer containing thousands of patient data sets, and is then used for targeted "personalized" treatment planning. However, solid evidence of a greater patient benefit is still pending. The road from research to practice appears to be longer than expected. Many renowned hospitals, for instance, abandoned the use of artificial intelligence and big data in the form of the IBM software "Watson for Oncology", in which cancer patients had placed great hopes, with disappointment. The risk of faulty treatment recommendations had been shown to be too high.

LITERATURE TIP

Fröhlich H et al.: From hype to reality: data science enabling personalized medicine
BMC Med. 2018 Aug 27;16(1):150. doi: 10.1186/s12916-018-1122-7.

Studies on medical devices: Proportion of RCTs is surprisingly high

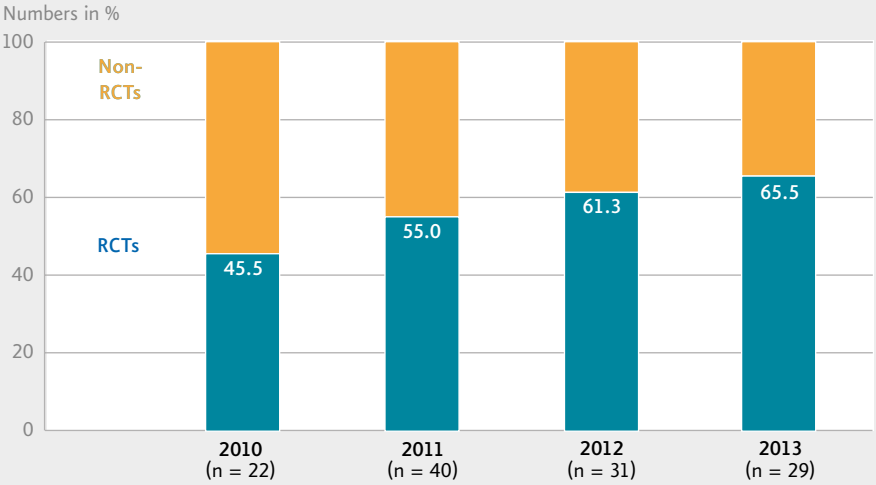
An analysis of applications for medical device studies revealed: Randomized controlled trials have become standard practice.

Surprising result. Compared with pharmaceutical studies, little is known to date about clinical studies on medical devices. To help address this issue, IQWiG conducted a sample analysis to evaluate applications for approval of clinical trials on medical devices, which in some cases yielded surprising results: The proportion of randomized controlled trials (RCTs) was clearly higher than experts had previously assumed.

122 applications were analysed. The Institute's staff analysed all application documents submitted to the Berlin Ethics Committee between March 2010 and December 2013, while maintaining confidentiality. 98 of the 122 applications were concerned with treatments, the remaining ones investigated diagnostics. CE markings were still pending for most of the tested products (75 of 122), which means they were not yet marketable. 57% of the studies in the whole sample had been planned as RCTs. At 70%, this proportion was even markedly higher in the 98 treatment studies and had continuously increased over the 4 years: In 2010, 63% of the treatment studies had been planned as RCTs; in 2013, the proportion was 86%.

Conclusion. A good third of the studies aimed at investigating a patient-relevant primary outcome. In many cases, they were even designed as blinded trials to ensure an informative recording of outcomes. This clearly goes beyond the current requirements to be met for a CE marking. About half of the studies were explicitly intended to prove not only safety or performance, but also efficacy. The analysis showed that RCTs on medical devices are feasible, and more than this, they have apparently become standard practice.

Proportion of RCTs in medical device studies is increasing



IQWiG 2018

Added benefit: Yes or no?

In Germany, each new drug undergoes an evaluation for approval before market entry, as well as a so-called early benefit assessment after entry.

AMNOG. With the 2011 Act on the Reform of the Market for Medicinal Products (AMNOG), the legislator introduced the term of added benefit into the Social Code Book V (SGB V §35a). According to this law, newly approved drugs containing new active substances have to be assessed for their added benefit directly after market entry (= early benefit assessment). All relevant data for this assessment are submitted in a dossier compiled by the pharmaceutical company. IQWiG produces a dossier assessment for the Federal Joint Committee (G-BA), which then decides on the added benefit of the new drug based on this assessment. This G-BA decision provides the basis for the pricing of the new drug.

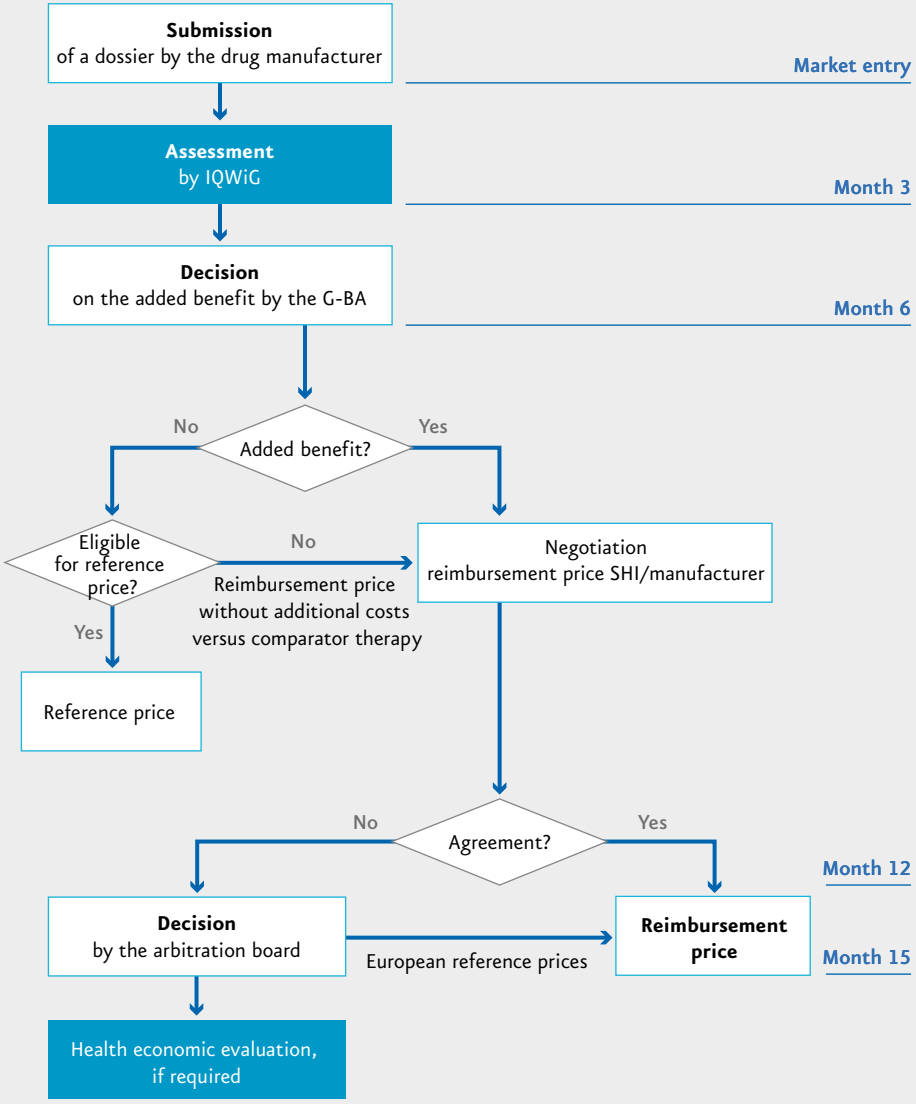
Added benefit. When a drug is approved, it is evaluated for its efficacy and whether its benefit outweighs its harm, so that it can in principle be used. However, this evaluation does not answer the question whether a new drug is better than, equal to, or even worse than drugs that have been used for years. This is where the AMNOG dossier assessment comes in. Its key component is the comparison with the so-called appropriate comparator therapy (ACT). Was disease duration shorter or survival longer? Were side effects reduced or was health-related quality of life improved? The answers to these questions are included in an overall assessment of the added benefit of a new drug.

Three months for the assessment. The Institute has three months to complete a dossier assessment. In this period, the opinion of external experts as well as the patient perspective are involved. The Institute may also conduct its own literature search to support the assessment (see flowchart on the right).

WEB TIP

IQWiG's methodological approach to the AMNOG assessments is described in its methods paper (version 5.0), chapters 2.1.3 and 3.3.3
iqwig.de > English version > Methods > Methods Paper

The AMNOG procedure



IQWiG 2018

Seven years of AMNOG: 272 drugs and 70 orphan drugs assessed

Balance after seven years of early benefit assessments: IQWiG produces additional addenda to 44 per cent of all assessments.

Since 2011, IQWiG has produced 272 drug assessments (according to AMNOG, see page 26f) and 113 addenda to these assessments (status: 31 October 2018). The number of the dossiers submitted differs from the number of the assessments, as some dossiers assessed different medical conditions (therapeutic indications). In those cases, each therapeutic indication counts as one assessment.

Addenda. IQWiG produces addenda if the pharmaceutical company subsequently submits supplementary documents in the commenting procedure after the dossier assessment or if the G-BA requests the assessment of additional aspects.

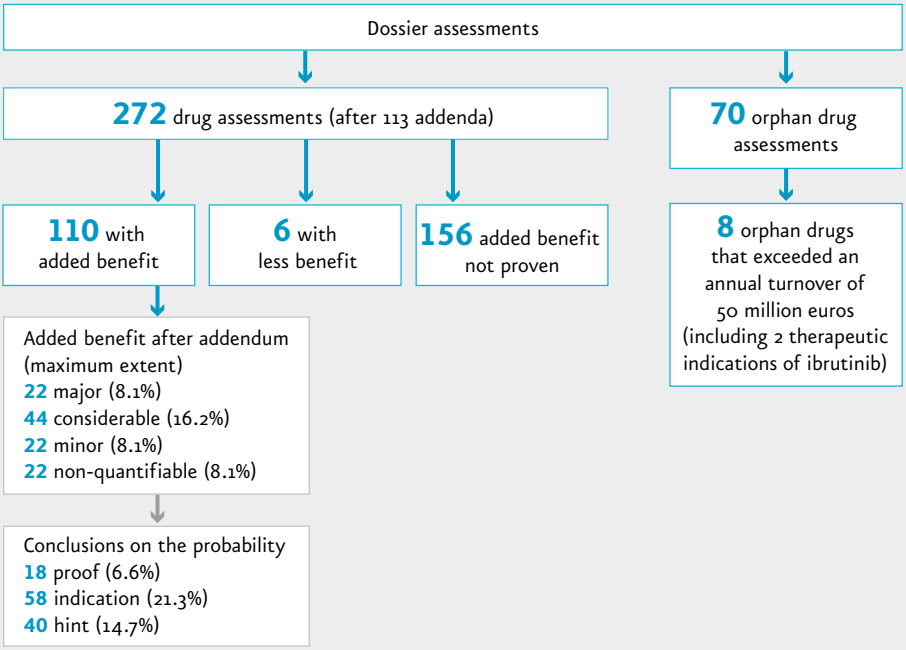
Extent of added benefit. The law (Regulation for Early Benefit Assessment of New Pharmaceuticals – AM-NutzenV §5 [7]) defines six categories to describe the extent of the added benefit. In decreasing order of weighting, these are:

- major
- considerable
- minor
- non-quantifiable
- added benefit not proven
- less benefit

Probability of added benefit. IQWiG's assessment of the probability of the added benefit, i.e. the certainty of conclusions of the data, is based on the available evidence. Depending on the evidence, the Institute differentiates between the following categories (in decreasing order):

- proof
- indication
- hint

Seven years of early benefit assessments: The results of IQWiG's assessments



IQWiG status: 31 October 2018

Orphan drugs. By law, the added benefit of drugs for rare diseases (orphan drugs) is formally regarded as proven at market entry. IQWiG then assesses the size of the target population in the statutory health insurance and the treatment costs. However, if the annual turnover exceeds the threshold of 50 million euros in the following years, a regular early benefit assessment is conducted.

WEB TIPS

Detailed information on the dossier assessments conducted by IQWiG can be found on

iqwig.de > English version > Projects & results > Projects

iqwig.de > English version > Projects & results > Publications

What and how often?

Between 16 November 2004 and 30 September 2018, IQWiG received a total of 795 commissions. In addition, 9 HTA reports have been selected for assessment from all topics proposed on the "ThemenCheck Medizin" website since 2017.

The general commission allows IQWiG to address and investigate issues of fundamental relevance; IQWiG has made use of this in 22 cases since 2004.

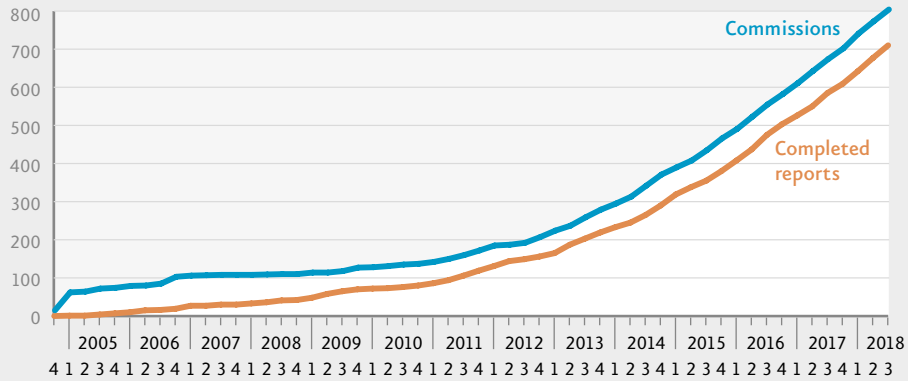
Projects completed since 2004

Addenda	144
Reports	122
Assessments according to §137h	8
Dossier assessments	334
Assessments of potential	35
Rapid reports	44
Other projects*	23

* Consultations on dossiers (14), commissions for health information products (8), and concept for a national health portal (1).

IQWiG, period covered: 16 November 2004 until 30 September 2018

Commissions and completed reports (totalled)



IQWiG, period covered: 16 November 2004 until 30 September 2018

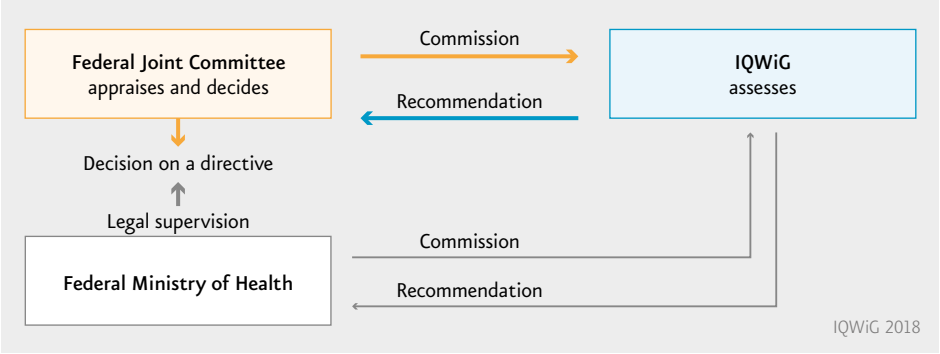
Who does what?

In Germany, several institutions are responsible for health technology assessment. This is regulated by law.

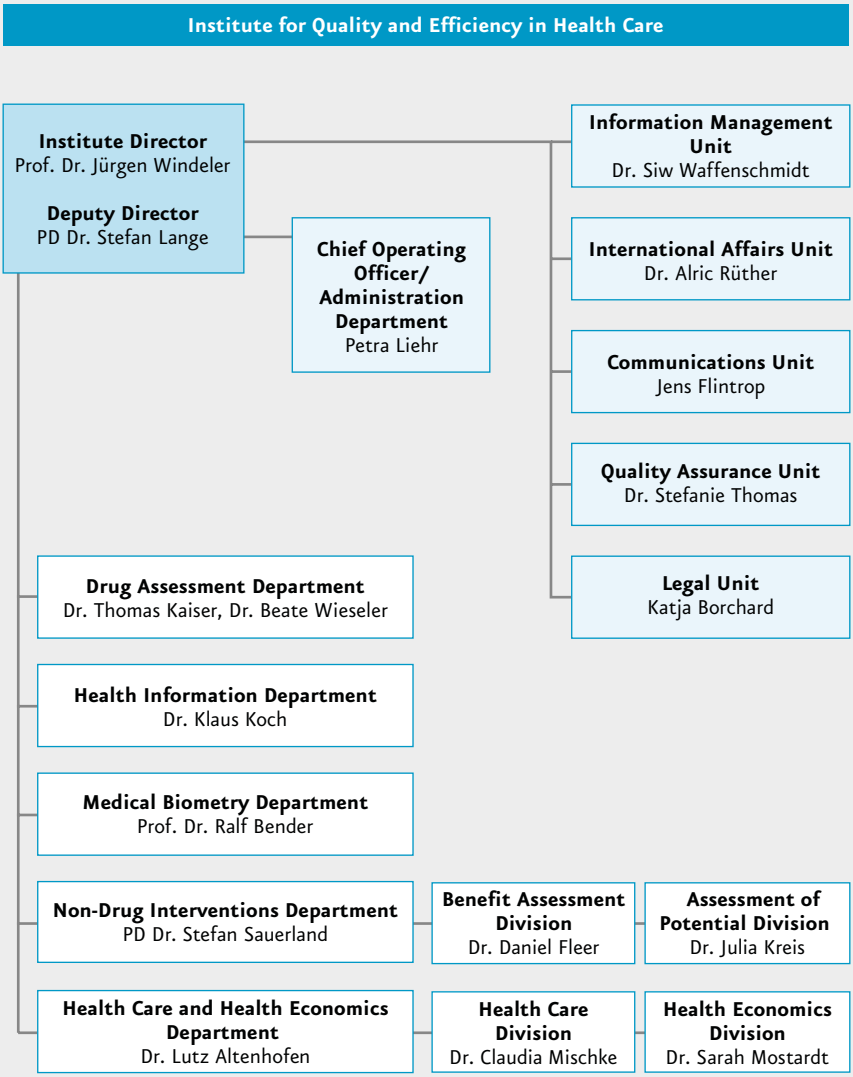
Independent assessments. As an independent scientific institute, IQWiG assesses the evidence on drug and non-drug treatments and diagnostic procedures. To a limited extent (general commission), the Institute itself can also identify and investigate topics or address those suggested by the public (ThemenCheck Medizin). Based on the evidence obtained, the Federal Joint Committee (G-BA) makes the necessary decisions for the health care of members of the statutory health insurance (SHI) funds. In the early benefit assessment of drugs, the G-BA decisions on added benefit are based on IQWiG's dossier assessments (see page 26ff), and provide the basis for the pricing of the new drug. Background information: About 90 per cent of the German population are SHI members.

Recommendations. IQWiG submits its assessments to the G-BA in the form of recommendations, which the G-BA has to take into account in its decisions. The G-BA publishes its decisions in a directive.

Commissioning agencies. Besides the G-BA as the main commissioning agency, IQWiG also receives commissions from the Federal Ministry of Health.



Structure of IQWiG



IQWiG 2019

Explanation of international abbreviations

General

HTA	health technology assessment
QALY	quality-adjusted life year

International HTA networks and organizations

EUnetHTA	European Network for HTA
HTAsiaLink	HTAsiaLink network
INAHTA	International Network of Agencies for HTA
ISPOR	International Society for Pharmaco-economics and Outcomes Research
RedETSA	Health Technology Assessment Network of the Americas

National HTA organizations

Australia

PBAC	Pharmaceutical Benefits Advisory Committee
MSAC	Medical Services Advisory Committee
PLAC	Prostheses List Advisory Committee

Belgium

KCE	Belgian Health Care Knowledge Centre

Brazil

CONITEC	National Committee for Health Technology Incorporation

Germany

G-BA	Federal Joint Committee
IQWiG	Institute for Quality and Efficiency in Health Care

United Kingdom

HPA	Health Protection Agency
PHE	Public Health England
JCVI	Joint Committee on Vaccination and Immunisation
NICE	National Institute for Health and Care Excellence
NSC	National Screening Committee

France

HAS	Haute Autorité de Santé

Italy

AGENAS	National Agency for Regional Health Services

Netherlands

ZIN	National Health Care Institute (former CVZ: College voor Zorgverzekeringen)

Norway

NIPH	Norwegian Institute of Public Health

Austria

LBI-HTA	Ludwig Boltzmann Institute for HTA

Sweden

NBHW	National Board of Health and Welfare
NLT	SALAR committee on new pharma-ceutical product therapies
SALAR	Swedish Association of Local Authorities and Regions
SBU	Swedish Agency for Health Technology Assessment and Assess-ment of Social Services
TLV	Dental and Pharmaceutical Benefits Agency

Spain

AETS-ISCIII	Institute of Health Carlos III

South Korea

NECA	National Evidence-based Health Collaborating Agency

Taiwan

CDE	Taiwan Center for Drug Evaluation

Thailand

HITAP	Health Intervention and Technology Assessment Program