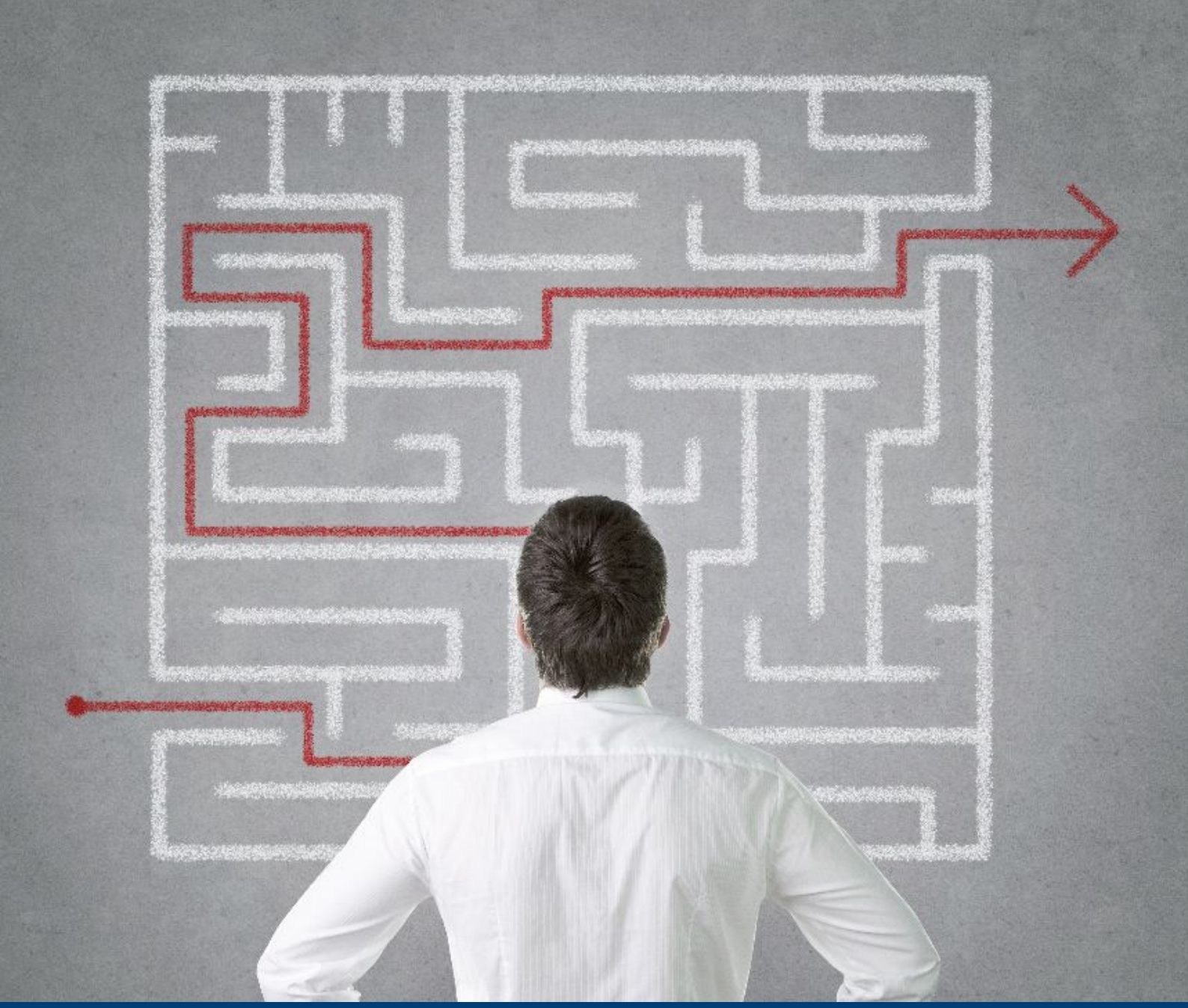

Publication series
INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

Volume 14
April 2022

Guidelines – their role in AMNOG and medical care

Springer Medizin

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Content

Goals of the plattform

Since the introduction of AMNOG in 2011, Germany has a well-established and widely accepted „adaptive system" for the assessment of the patient-relevant additional benefit (Health Technology Assessment, HTA). The assessment of the additional benefit by the Federal Joint Committee (G-BA) is the result of expert work based on a law (AMNOG) and procedural and methodical regulations.

The active players on the side of the G-BA and the health insurance funds are classified as scientists, hospital physicians and office-based statutory health insurance physicians, the Medical Service of the Health Funds and employees of the insurance fund administration, but also as patient representatives, however, they act on the basis of their own interests. Value dossiers for new pharmaceuticals, likewise qualified and interest-based, are submitted to the G-BA by the pharmaceutical companies, which serve as the basis for the assessment of the additional benefit.

Because the supply of pharmaceuticals to the population is significantly influenced by the assessment of the additional benefit, it makes sense to provide critical and careful support for the assessment process with a focus on identifying possible faults and counteracting imbalances. The Interdisciplinary Platform on Benefit Assessment set itself the task of supporting the benefit assessment within a small group of experts with the following objectives:

- Discussing the procedures for the assessment of the additional benefit, including in relation to approval of pharmaceuticals,
- Working towards international standards of evidence-based medicine and of health economy being adhered to as well as applied and further developed,
- Determining whether and to what extent patient-relevant additional benefits, in particular in the areas of mortality, morbidity and quality of life, are identified and which methodological problems occur during the process,
- dentifying possible undesirable developments, in particular with regard to supplying patients with new active substances,
- Enabling and holding a constructive dialogue with all players involved in the benefit assessment procedure, e. g. on the further development of the legal framework conditions of AMNOG.

Moreover, the European perspective in HTA of innovative pharmaceuticals was reinforced by the European Commission's proposal for a Regulation on HTA in 2018. Monitoring the conflict between the well-established national assessment and the intended European HTA harmonisation is also a central concern of the platform. The Interdisciplinary Platform would like to make a contribution to ensuring that new active substances are transparently and fairly assessed. According to the Advisory Council, an interdisciplinary dialogue about the results of the assessment and the applied benefit assessment methods is essential. Furthermore, in the benefit assessment process it sees a good opportunity to inform the prescribing physicians of the expected additional benefits of new pharmaceuticals for patients earlier than it was previously the case.

The Interdisciplinary Platform is a result of the discussion process between clinicians and experts. The mutual desire to pool specialist knowledge in the form of interdisciplinary seminars is supported by an open consortium of sponsors. These include AbbVie Deutschland GmbH & Co. KG, DAK Gesundheit, MSD Sharp & Dohme GmbH, Novo Nordisk Pharma GmbH, Roche Pharma AG, Association of Research-Based Pharmaceutical Companies (vfa e.V.), and Xcenda GmbH.

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

Guidelines: Guidance for research, care and benefit assessment

Professor Jörg Ruof

Dear readers

every cover of our publications is selected by the platform's advisory board. This time, the preference was clear: the labyrinth. The intuitive persuasiveness of this symbol in the context of the guideline topic of the current issue may have various causes, such as:

- The search for orientation in an increasingly complex scientific and therapeutic environment;
- the orientation of the respective decisions of the G-BA or also of the attending physicians on the Ariadne's thread of clinical evidence;
- the ever-present risk of a costly and potentially harmful aberration for patients;
- or also – in reference to the functional significance of the labyrinth in the human inner ear – the effort to maintain a healthy, living balance between benefits and risks, freedom of therapy and guidelines for action, or also topicality and the indispensable scientific care in the preparation of guidelines.

All these aspects are reflected in the articles of this publication.

We start with the view on the guidelines from the perspective of politics. Michael Hennrich and Martin Roth discuss the appreciation and support for the enormous commitment of the scientific medical societies, preservation of all stakeholders' independence – who often work on a voluntary basis – and the use of the possibilities of digitisation, especially in the weak point of updating guidelines.

Antje Behring then reports on the promotion of guideline work within the framework of the Digital Care Act. This funding, which is welcomed by all sides, is accompanied, among other things, by the demand to preserve and strengthen independence, optimise evidence research, topicality, as well as better processing of recommendations for action in the case of an uncertain data situation.

The articles of Ina B. Kopp and Corinna Schäfer allow a deep insight into the status quo of guideline work in Germany and provide an outlook on the fields of development and future tasks. In the next article, Corinna Schäfer presents the major quality criteria and high-quality standard in the preparation of the S3 guidelines and the national health care guidelines. The accountability of medical science plays a key role in this context. As head of the Institute for Medical Knowledge Management of the Association of the Scientific Medical Societies (AWMF), Ina Kopp has been coordinating the preparation of guidelines at a crucial point for many years.

The steady increase of high-quality S3 guidelines over the years demonstrates the enormous commitment of the 180 scientific societies that are members of the AWMF. The transfer of this guideline knowledge into „living guidelines", into a progressive, iterative life cycle, currently presents a central challenge. Therefore, the AWMF is developing and implementing appropriate digital formats.

The articles of Julia Wagle and Klaus Schlüter address the importance of guidelines from the industry's perspective. The consensus is the support of high-quality guidelines as well as the adjustment of patient care, benefit assessment procedures and planning of clinical trial programmes based on high-quality guidelines. However, the still reluctant use of guidelines in clinical practice or lack of a current S3 guideline in about half of the benefit assessment procedures should be seen critically. The importance and development of European guidelines for the German AMNOG process is also addressed by the industry.

On centrepiece of this publication is the practical guideline reports from oncology, cardiology, and intensive care medicine.

- Bernhard Wörmann addresses the specific challenges of

oncology. When a guideline is published, some recommendations are already no longer up to date due to the fast innovation cycles. The guidelines of the Working Group on Gynaecological Oncology, for example, which are updated very promptly and at a high-quality level, or the Onkopedia guideline programme of the DGHO, which takes a median of six months to develop a guideline, take a pioneering role in this respect.

- Using the example of the guideline on atrial fibrillation, Paulus Kirchhof describes the development of guidelines in cardiology. Both European and international cooperation has top priority here. Especially in view of the centrally coordinated approval of new pharmaceuticals by the EMA and the increasing Europeanisation of benefit assessment, this international collaboration in the development of cardiology guidelines seems to be trendsetting.
- The AWMF COVID Task Force has successfully developed high-quality guidelines. Christian Karagiannidis impressively describes the learning process of the task force from the first S1 guideline in June 2020 to the publication of the first S3 guideline in February 2021. This article shows the fascination about the scientific progress, the enormous commitment of the experts involved, but also the need for structural reinforcement of this activity.

This publication concludes with an article of Dimitra Panteli from the European Observatory on Health Systems and Policies. Especially against the background of an increasing Europeanisation of benefit assessment, it becomes clear once again how important it is not only to have one of the leading European guideline systems in Germany, but also to increasingly shape and develop these processes together with the European partner countries in the future.

In this sense – dear readers – we hope that this short red Ariadne thread of this publication has aroused your interest in reading all the interesting articles. Enjoy reading this publication.

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A view on guidelines from the Parliament's perspective

Michael Hennrich, Member of the German Bundestag, and Martin Roth

Based on the principle of self-governance, the German healthcare system has various assessment and regulatory instruments to ensure evidence-based treatment of patients. Guidelines play an important role here. The institutional independence behind guidelines deserves political appreciation and support. Stakeholders from politics and self-administration are called upon to further develop the guideline system together. For this purpose, existing cooperation forms between institutions can be used, especially on the part of politicians, to develop further offerings. The goal must be to make medical knowledge more up-to-date and make it more widely available in digital form for the best possible treatment of patients.

Let's start with a change of perspective: Do we even need a political view on guidelines? They are developed by scientific medical societies according to such standards. They serve physicians as legally non-binding guidelines for treatment decisions. At an individual level, they are linked to improved chances of recovery. At macro level, they help to structure the treatment range. But where should politics normally derive a mandate for action for itself at this medical-scientific level?

Striving for sound knowledge versus determining generally binding rules for our society – the crisis of the pandemic has reminded us quite acutely that science and democratic politics function according to different rules. One criterion for a functioning democratic system in this sense is that scientific findings are considered in the political decision-making process and not vice versa.

However, political issues arise one level behind: in resources and structures for the development of guidelines according to scientific standards to relate them to existing evidence tools and treatment specifications. And finally the legal framework and financing solutions must be further developed, the tremendous medical progress must be implemented into patient care on a timely basis, and the potential of digitisation must be exploited.

While role can the political players play in all these issues to ensure that patients receive the best possible therapy? This article addresses a few of these points.

Freedom of therapy, directives, benefit assessment – where do guidelines stand?

The therapeutic freedom of the medical profession and its freelance nature deserve a firm place today and even more in future scenarios of a more digitised and data-driven medicine. As a treatment provider and trusted partner of pati-

ents, the independent physician should remain a key point. At the same time, freedom of therapy does not mean an arbitrary therapy. Court decisions, for example, are based on the medical standard at the time of treatment. The following applies here: „Guidelines do not replace expert opinions. Although in individual cases they may accurately describe the medical standard for the time of their enactment, they may also develop standards of medical treatment or become obsolete in their turn".[1] Legally, this is ambiguous. However, they still serve as a reference value in liability law or the work of the medical service.

Should this ambiguity be addressed by means of a stronger legal standardisation? One argument for this could be that an effective instrument also needs a clear standardisation of its use.[2] However, an unambiguous and even partly conclusive regulation is not easy to find and would raise new questions. Government commitment would be needed to establish new institutions. How could we ensured in a different organisational form that volunteer expertise is still integrated into the work? And if the federal government created its own institution, which resources would be required and where would they come from? And finally, how could the scientific independence of such an institution be ensured in the long term – a question that has already been raised. Thus, it is quite questionable whether this would lead to a better result. This should also be examined on an international basis.

However, such a step does not seem necessary. In completely different policy areas, legislative reluctance has also proven its worth. One example is the collective bargaining autonomy which the legislator does not touch for historical and political reasons. Development primarily through judicial decisions remains a viable path, especially when it depends very much on the individual case.

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Martin Roth *studied political science and law and has worked as a research assistant in the German Bundestag since 2016. After a previous employment, he joined Michael Hennrich's office in 2019, where he is now responsible for pharmaceutical policy issues.*

If freedom of therapy is on one side of the spectrum, directives issued by the Federal Joint Committee (G-BA) are on the other. Directives have an imperative character, and their elaboration is more formalised and standardised. The ministry reviews them and can object or request further information or a statement from the G-BA or impose conditions (section 94 (1) SGB V). Directives also provide guidance for quality issues, such as minimum volume regulations for hospitals (section 136b, para. 1, sent. 1, No. 2, SGB V). In all these, they are considerably different from guidelines.

Policy should be evaluated on its ability to find graduated solutions for different problems. Directives and guidelines are different and complement each other as instruments. They reflect the width of the regulatory spectrum of active self-governance under government control. Their coexistence also provides the opportunity to initiate developments, which is the case in practice.

The evaluation of pharmaceuticals should also be examined. Hence, guidelines become important in the evaluation of the appropriate comparative therapy (ACT). The legislator has recently approached the work of the G-BA and the guideline system.

Section 35a (7) SGB V was expanded with the Act for Greater Safety in the Provision of Medicines (GSAV).[3] The G-BA and the Association of the Scientific Medical Societies (AWMF) created the possibility of a consultation with the professional societies. So far, the parties involved describe this activity – which is not remunerated – as quite time-consuming. Moreover, the question arises as to which extent the assessments will be taken into consideration in the end. Both points should be reviewed and regulated by law, if necessary.

The weak point of updating

Updating is a weak point of guidelines which is associated to the allocation of resources. The ACT is based on the current standard of care. The fact that it takes several years to complete a guideline in some areas and updates only take place in cycles of three to four years affects the importance of guidelines in the process. A restricted look at S3/S2e guidelines in the context of benefit assessments substantiates this problem: On average, three years (between 8 and 78 months) lie between the research of the guideline and the G-BA decision.[4]

On the other hand, innovative pharmaceuticals can also significantly affect the therapeutic standard making an update of the guideline necessary. How can the increasing pace of innovation be considered? As one business partner put it in an email: „We need the ‚S3 tankers,' but we also need the ‚Onkopedia speedboats'" or alternative concepts, such as living guidelines. This needs to be addressed, also by politicians.

There are often discrepancies between AMNOG decisions and guidelines.[5] But can we draw conclusions for the political level? In general, we should keep in mind that the two instruments are based on a different logic. On the one hand, the AMNOG is designed as a pricing and cost saving tool to ensure fast availability of innovative pharmaceuticals. On the other hand, it is intended to „separate the wheat from the chaff" i. e. to distinguish new pharmaceuticals with real added value from those without.[6]

Well, it does justice to both. In terms of methodology, it is intended to make a statement on the additional benefit of a pharmaceutical as compared to a specified ACT and not on its individual therapeutic value in the treatment cascade. For the AMNOG, the legislator stipulated that all relevant data must be submitted and published, including those that were previously not accessible to the public. Guideline authors should make more use of this treasure of data from the AMNOG.

Thus, both tools have their strengths and right to exist. By anchoring AMNOG decisions in the physician information systems by legal prescription, AMNOG decisions are also more present than before.[7] They are increasingly used in daily clinical practice. Development would be problematic if systemic, rather than medical, reasons led to strengthening a certain tool at the expense of the other or if different assessments led to structural distortions in care.

It will remain a challenge for politics to monitor and evaluate this. A stronger and more systematic exchange between the tools provides the opportunity to take the best from the different approaches and objectives of the procedures and increase dynamics. Medical progress is tremendous and takes place by leaps and bounds, as innovations in advanced therapy medicinal products (ATMPs) show and we all recently experienced with mRNA technology.[8] It must be a political concern and ethical imperative that it reaches patients quickly and affordably. Against this background, e.g. post-market data collection (section 35a para. 3b SGB V) for promising pharmaceuticals was implemented in the last legislature with reference to the AMNOG procedure, albeit with a thin database.

Variations between assessment tools with different strengths can be a starting point to ask the right questions and keep bringing patient care up to the scientific level time and again.

Structures and resources

AWMF plays a central role with a lot of work in the preparation of guidelines. It acts as an arbitrator in methodological questions, as bureaucratic institution for the guideline development process, as advisor and coordinator of the 179 plus three associated professional societies, as well as as operator of the guideline registry.

A look at the annual report 2020 shows 455 comments from authorities and 775 publications in the guideline registry, including 140 newly published guidelines and a total of 202 S3 guidelines. Other tasks include collaboration on licensing regulations, consulting activities e.g. for the Institute for Quality and Efficiency in Health Care (IQWIG), the Federal Institute for Drugs and Medical Devices (BfArM) or at hearings in the German Bundestag, collaboration in the AMNOG process, as well as other activities.

For this purpose, the AWMF has nine employees, seven of whom work directly in the Institute for Medical Knowledge Management (INWI), which is responsible for guidelines. Even without going into depth, this brief comparison raises the urgent political question of whether the available resources are sufficient and how they could be further strengthened.

One possibility are further collaborations: Last year, the IQWIG supported professional societies with evidence research on six selected topics to develop or update guidelines. The legal basis for this is the Digital Care Act that came into force in 2020. This collaboration relieves the workload of the professional societies while preserving their sovereignty over the guidelines. This support frees up resources to accelerate guideline development in consideration of a broad evidence.

Of course, the question of funding is a major issue. The AWMF as a registered association is financed by the medical societies depending on the number of members. The medical societies, in turn, co-finance the development of medical guidelines from their membership fees. In addition, they receive donations e.g. from the German Cancer Aid Foundation. As vivid proof of an independent medical research landscape and a committed society, such structures may be welcome.

However, the question arises as to whether grants and donations, as a second pillar alongside membership fees,

provide a sufficiently sustainable structure. With estimated average costs in the six-figure range for the development of a guideline, doubts appear justified. For future debates, more transparency about the cost structure and individual cost items should substantiate political claims with concrete figures.

The third pillar is allocations from the healthcare system through third-party funded projects and ongoing agreements. An additional funding modality was created with the Digital Care Act (DVG). Over the next five years, five million Euros will be invested annually with funds from the Innovation Fund in guidelines for subject areas that are not adequately covered. Successful collaborations of self-governing institutions and professional societies are the best advertisement for further funding approvals.[9]

The political debate on the advantages and disadvantages of project-based funding models has been going on for some time in all policy areas. Particularly in recent years, there has been a shift in many points about how to make funding models more sustainable. E.g. if we discuss about financing civil society structures in rural regions, we should also consider issues of guideline development.

Appropriate funding models must be developed here. Even in case of state funding, the AWMF's and professional societies' independence should be preserved. Structural support as a fourth pillar could thus be used as an additional model to membership fees thus rewarding successful networking of the voluntary commitment or as a subsequent step to successful third-party funding applications. A first step could be payment or better payment, respectively, of consultations by the AWMF. Many solutions are possible here.

The funding issue also plays a central role for the digitisation of guidelines.

The amount of information and the possibilities of digitisation suggest a different approach to knowledge, such as living guidelines: faster availability, faster updating, prepared along structural data models. The guideline system has also taken this path. Currently, there is a tendency toward isolated solutions. One example is the Onkopedia project of the German Society for Haematology and Medical Oncology (DGHO) and its app-based offer.

In Germany, there is a tendency to plan digitisation projects too far in advance and too precisely instead of proceeding iteratively and further developing things that work. The tendency to block each other is also particularly pronounced in the healthcare system. In this sense, anything that works and is used is generally positive. However, the declared goal of transferring the entire guideline registry into a digital structure should not be lost sight of. It needs and deserves support from politics.

Single-digit million investments seem to be required to create a basic digital structure. Due to the long-term benefits, these funds should be available. The impetus to tackle this in concrete terms and come up with a concrete plan lies in the responsibility of the guideline stakeholders. Politics would be well advised to pick up the ball.

Freedom of interest as a sustainable success factor

Trust in the independence and freedom of interest of the institutions and individuals developing or contributing to guidelines is as important as the underlying scientific expertise. Transparency and freedom of interest – demands that are also made on politics – are of key importance for the AMWF and the professional societies. Several interest management mechanisms have been established for this purpose. There is an online portal for individual declarati-

ons of interest, including step-by-step consequences in the event of an overlap.

In addition to being excluded from projects, experts can still participate in the preparation of guidelines, but e. g. without voting rights. The public can access the guideline registry and submit comments. Professional societies make guidelines available for public consultation. The website and the association Leitlinienwatch.de as a professional observer also make it clear that the medical community recognises the relevance of the topic. These are all important points, but are they sufficient?

Voluntary work, organisational forms under association law, participation processes with many stakeholders and, at the same time, concrete interests of third parties – this mixed situation makes it clear that the guideline system is vulnerable in terms of freedom of interest and transparency. Often, misconduct of individuals is enough to discredit a whole community and its organisation. The problem is well known in the political arena! Whether all feasible and target-oriented measures have already been taken at guideline institutions, where there is still potential for improvement – these questions must first be answered by the respective stakeholders. Of course, these questions are considered highly relevant for political decisions, especially with a view to future decisions on the question of financing and tasks.

Experiences from the Corona pandemic

Crises reveal what works and what doesn't. This was also the case in the Corona pandemic. Disputes over competencies, small-scale regulations, communication errors, gaps in digitisation and information processing – to name just a few deficits. On the other hand, there are also many positive aspects: First and foremost, the healthcare system should be mentioned which has always functioned when it mattered. At the beginning of the pandemic, the threat was intensified by a lack of clarity and knowledge. This debate, which was strictly medical in nature, was soon followed by a discussion on how society should deal with the pandemic. The latter then developed into the greatest challenge in overcoming the pandemic so far. Expected translation hurdles from scientific findings to societal action, as well as major distortions, untruths, and conspiracy ideologies, persist two years after the outbreak. On all these issues – from acute treatment to vulnerable patient groups to the use of masks to the operation of schools – guidelines with different levels of evidence provided clarity and guidance.[10]

As a scientific and, above all, neutral source, guidelines have thus made a medical and a socio-political contribution to containing both the pandemic and false news. The people who developed them deserve our thanks. They have helped us to better cope with this health crisis. The independence and performance of the „guideline system" should remain on the credit side of the pandemic's balance sheet.

Conclusion

We place the highest demands on our healthcare system: solidarity-based patient care at the highest level, the principle of economic efficiency and, at the same time, openness to innovations that should reach daily clinical practice on a timely basis. The principle of self-governance presents an organisational principle that is unusual as compared to international standards yet very successful. It is based on a network of institutions and rules that have evolved over time, in which the state provides the guidelines but is not the sole guarantor of action.

If we want to continue to rely on these principles in our healthcare system – and despite all obstacles there are ma-

ny reasons for it – we should also be aware of the following facts: politics depends on preconditions that it can neither prescribe nor create itself.

Guidelines illustrate this particularly well, and this article wants to emphasise this. More guidelines on more topics, with increasing evidence-based quality, that are digitised, developed even faster, and updated more quickly – whoever agrees on these claims should think about ways and means to support the guideline system without jeopardising its independence. Health policy faces the challenge of providing support and binding regulation, while at the same time being aware of the limits of its own scope for action.

References

[1] BGH, decision of 15 April 2014 – VI ZR 382/12 - key statement, and RN 17f. = GesR 2014,404-408.

[2] Apart from § 137f SGB V, Structured treatment programmes for chronic diseases, in which guidelines are mentioned as reference points to be considered, they are not further mentioned or standardised in the SGB.

[3] Excerpt §35a paragraph 7 SGB V: „Zu Fragen der Vergleichstherapie sollen unter Beachtung der Betriebs- und Geschäftsgeheimnisse des pharmazeutischen Unternehmers die wissenschaftlich-medizinischen Fachgesellschaften und die Arzneimittelkommission der deutschen Ärzteschaft schriftlich beteiligt werden." (On questions of comparative therapy, the scientific medical societies and the Drug Commission of the German Medical Profession should be involved in writing, while respecting the trade and business secrets of the pharmaceutical entrepreneur.)

[4] Kaiser T. „Studienergebnisse zu neuen Arzneimitteln – Wie unterscheiden sich Leitlinien von der Nutzenbewertung?" (Study results on new medicinal products - How do guidelines differ from benefit assessments?). PowerPoint presentation, 29 March 2019.

[5] Frick M. „Eignet sich die Zusatznutzenbewertung für das Arztinformationssystem?" (Is the additional benefit assessment suitable for the physician information system?), PowerPoint presentation, 19 April 2018.

[6] Federal Ministry of Health (ed.), Separating the wheat from the chaff; the German Pharmaceutical Market Reorganization Act (AMNOG), Berlin 2010.

[7] The legal basis is the German Act on Strengthening Pharmaceutical Supply in Statutory Health Insurance (AMVSG) which came into force on 13 May 2017, and the Electronic Medicines Information Regulation (EAMIV) from August 2019. The implementation is taking place in stages.

[8] At present, 13 ATMPs are approved and available in the EU, and another five have been withdrawn from the market for economic reasons. At present, more than 1,000 studies in various stages are conducted worldwide. Both rare and common diseases are researched. If only a small proportion will be successful, the chances of a cure will be associated with major funding challenges.

[9] Press release: Innovation Committee funds 52 new projects in health services research – for the first time also concepts on medical guidelines, retrieved from: https://www.g-ba.de/presse/pressemitteilungen-meldungen/976/, accessed on 15 December 2021.

[10] At present, there are 18 guidelines at different levels of evidence for the prevention and treatment of corona, and another seven are in progress. See also the article by Professor Karagiannidis on this topic.

Promoting and challenging guidelines – the view of the Federal Joint Committee

Dr Antje Behring | Head of the Department Pharmaceuticals for Early Benefit Assessment at the Federal Joint Committee (G-BA)

Medical guidelines increasingly serve as an information base for decisions in public healthcare. This places high demands both on the quality of the statements and methodological quality of guidelines. To ensure that these high requirements are met – against the background of many issues that must be addressed in a guideline – independent superordinate support is needed. The Digital Health Care Act has set the course for this. It is appreciable that certain quality requirements are placed on the statutory support in the development of guidelines. From the G-BA's perspective, this also includes ensuring that public sources of information, such as clinical data on new pharmaceuticals provided on the G-BA's website, are also subject to the evidence assessment. It will only become apparent after a few years to what extent the independent funding has contributed to enhance the quality of the evidence base as well as the timeliness of the guidelines and expand the guideline portfolio. Ultimately, it is important that guidelines are used and distributed based on their medical value. This can promote the advancement of medical knowledge among professionals and improve patient care.

1 Guidelines: Status quo

Medical guidelines have long since simply served as clinical guidelines for physicians. According to the definition of guidelines on the AWMF[1] website, guidelines are systematically developed statements that reflect the current state of knowledge to support the decision-making of physicians and members of other healthcare professions and patients/citizens to provide appropriate care for specific health problems.

Moreover, guidelines generally serve decision-makers as a starting point and essential basis to translate recognised recommendations for action and care pathways into more far-reaching regulations and justify them.

In order to fulfil this important function, users must be confident that the information compiled corresponds to the current state of knowledge and has been systematically researched. Moreover, the results must have been transparently evaluated according to recognised methodological standards after reviewing the evidence including all uncertainties. All this information on methodology and conflicts of interest must thus be accessible to readers – as must the underlying literature – to be able to assess the quality of the respective guideline.

In addition, medical guidelines do not only contain information on the prevention, diagnosis, and treatment of a disease, but also provide information on quality standards, care paths, practical conditions and, in some cases, key points on legal, ethical, social, and economic conditions.

Thus, a medical guideline is not just one systematic review on a specific topic. Depending on the research question, up to a hundred systematic reviews may have to be prepared to meet the requirement of a systematic weighing of benefits and harms for the final recommendation of a guideline.

The required financial and human resources are extensive and cannot be left to dedicated experts alone but require independent superordinate funding and support from independent institutions with appropriate competence and expertise.

2. Independent funding of guidelines

Since 2019, the Digital Health Care Act (DVG[2]) has created the possibility to fund guideline work on an independent basis. On the one hand, revision and development of new guidelines can be funded by the Innovation Fund of the Federal Joint Committee (G-BA), and on the other hand, the Institute for Quality and Efficiency in Medicine (IQWiG) can be commissioned by the Federal Ministry of Health (BMG) to systematically research the evidence on specific questions arising from guidelines.

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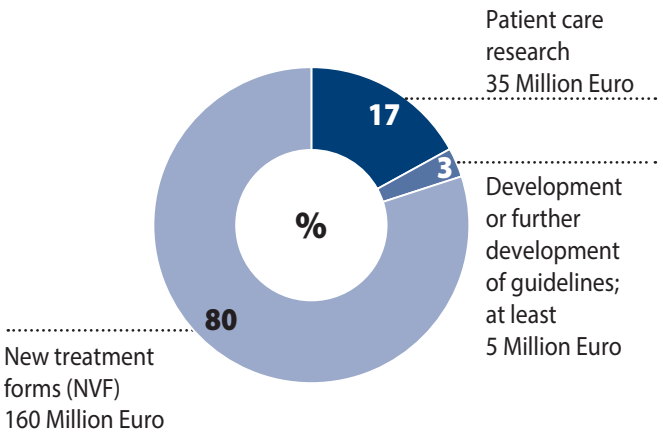
Annual funding amount under the DVG for 2020–2024



Source: J. Hecken, Vortrag auf der 30. Leitlinienkonferenz der AWMF, 13.12.2019

Figure 1: With the Digital Health Care Act (DVG), the G-BA can fund guideline development or revision.

Funding by the Innovation Fund

The annual funding amount provided by the Innovation Fund (from healthcare research) should be at least five million Euros for the promotion of medical guidelines corresponding to some three percent of the total amount (figure 1).

Depending on the type of project, the following funding period should not be exceeded:[3]

- maximum of 30 months for: development of a new guideline with S3 classification or further development of an existing guideline into a guideline with S3 classification;
- maximum 36 months for: revision of a guideline with S3 classification to a „living guideline" with annual review and update;
- Maximum 18 months for: Updating a guideline with S3

classification.

For example, in the 2020 funding period[4]

- 11 projects on the topic „Treatment of rare diseases;
- 8 projects on the topic „Treatment of people with mental illnesses and complex treatment needs";
- 4 projects on the topic „Prevention and treatment of infectious diseases, in particular to strengthen appropriate antibiotic therapy and contain antimicrobial resistance" were funded.

These included e.g. development of a guideline on the diagnosis and treatment of glomerulonephritis; a guideline on the diagnosis, treatment, and rehabilitation of people with severe impairment of personality function; and the update of the guideline on the management of bacterial, outpatient and inpatient acquired urinary tract infections in adult patients.

According to the funding announcement of 7 June 2021, the following topics will be funded in the next funding period:

- treatment of rare diseases;
- treatment of more common diseases, treatment of risk factors for non-communicable diseases, multimorbidity, and improvement of safety of pharmacotherapy (AMTS) in healthcare;
- treatment of target groups with special needs (e.g. children, adolescents, elderly and/or people in need of care);
- surgical interventions on the skeletal/musculoskeletal system.

Support of evidence research by the IQWiG

The responsibilities of IQWiG have been stipulated in the German Social Code, Book V (Section 139a, para. 3). The Institute is engaged in issues of fundamental importance, including research of current medical knowledge as a basis for the development or further development of guidelines. The order portfolio was supplemented by the DVG in section 139b providing the possibility for the AWMF to propose topics for the development or further development of guidelines to the BMG in cases where the institute is commissioned with research. The funding requirement for these guideline topics can amount to up to two million Euros annually from funds for financing the Institute.

One of the first orders of the Federal Ministry of Health (BMG) was the evidence research for the update of the interdisciplinary S3 guideline „Dementia" for which the German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology (DGPPN) and the German Society for Neurology (DGN) are responsible as professional societies. This project illustrates the importance and scope of the background work in the development of the guidelines.

The evidence search for the S3 guideline on dementia includes six evidence reports:[5]

- cognitive training/cognitive stimulation;
- technical support systems;
- dementia care management;
- structural imaging;
- non-pharmacological interventions for minor cognitive impairment and biomarker detection;
- structural education about the initial diagnosis.

Neutral processing of the existing evidence may reveal clear evidence gaps that cannot be determined within the scope of the clinical practice. E. g. the result of the information acquisition on the question of structural imaging is that the evidence searches for the S3 guideline on dementia brought more than 1,500 publications on the topic, but none of them was methodologically suitable to answer the research question. This means that despite many reports about advanced differential diagnostics using structural

imaging, no adequate study has been published comparing this method with diagnostics without advanced differential diagnostics in patients with mild to severe dementia.

For decades, scientists have called for independent funding and professional support for guideline work, including essential preparatory work, to minimise interest-driven guideline development and influence on recommendations for action, especially via funding from the pharmaceutical industry.[6,7]

3. Role of guidelines in the G-BA

The Rule of Procedures of the Federal Joint Committee (G-BA) mentions methodologically high-quality guidelines at various points. Particularly noteworthy are the procedures for the evaluation of medical methods, guidelines on outpatient specialist care, and disease management programmes (DMPs).

For example, chapter 2 of section 31 (evaluation of medical methods and testing) describes how a new theoretical-scientific concept (as defined in section 137h (1) sentence 2 of the German Social Code, Book V) is to be distinguished from an established systematic approach that has already been introduced into inpatient care, with the aid of methodologically high-quality guidelines. As a further example, guideline decisions on outpatient specialist care (ASV, section 116 b SGB V) are cited, in which the uniform care of patients requiring highly specialised services, for example because they suffer from rare diseases, is regulated by outpatient contract physicians and hospital outpatient departments (see chapter 3 (ASV) section 2 VerfO G-BA).

The importance of guidelines in the development of directives for the requirements for the design of structured treatment programmes in accordance with Section 137f SGB V becomes particularly evident in chapter 6, section 4 of the G-BA Regulation. The guideline search, selection of guidelines, their assessment as well as the extraction of information from these guidelines, are essential procedural steps. Since the requirements described in these guidelines are intended to particularly relate to those aspects of care for which there are reasoned indications of relevant deficits in care, it is even more important that the measures must be based on evidence in order to eliminate these deficits. Primarily guidelines are considered that have been developed within the scope of a systematic development process in accordance with the principles of evidence-based medicine.

In addition, in other procedures, such as the definition of requirements for quality-assured use of advanced therapy medicinal products (ATMPs), guidelines are referenced to define quality-assured application requirements for the pharmaceuticals or to be able to define measures that ensure the safe and effective application of the therapies.

From the G-BA's point of view, it would also be desirable to position the structural requirements, such as qualifications of the specialist staff, availability of instruments and equipment, or information on interdisciplinary cooperation, to ensure quality-assured treatment of the disease and promote the quality of care.

In some cases, it is difficult to derive specific quality indicators from the guidelines to make the implementation of the guideline recommendations measurable.

It is important that the evidence base is systematically prepared and made known so that the guidelines can be used as a basis for decision-making. In case of heterogeneous studies, insufficient or missing evidence, it must be possible to derive both conclusions and reasons for the recommendations made. On the other hand, recommendations for action that are not associated with any source of

evidence and derivation of the decision are problematic.

One example is the strong recommendation to perform a resting ECG with twelve leads in patients with a suspected coronary artery disease (CAD) that has been based on medical history and findings.[8] The NVL CHD clearly stipulates that the evidence is weak, but the rationale for the nevertheless strong level of recommendation remains vague.

It is also problematic when publicly available documents that are also relevant to the user of the guideline seem to come to different conclusions from the same evidence base. Consequently, the reader must deal with dissenting positions in the decision-making process.

4. Guidelines in the early benefit assessment of new active substances

Since the German Pharmaceutical Market Reorganization Act (AMNOG) came into force in 2011, every new pharmaceutical with a new active ingredient must undergo an additional benefit assessment as compared to an appropriate comparative therapy (ACT). Thus, the examination of current therapeutic options in a wide range of indications is systemic for the early benefit assessment. Particularly for the determination of the ACT, which must represent the generally accepted therapeutic standard in the respective indication area, guidelines serve as an authoritative source to provide an overview of non-pharmacological and pharmacological evidence-based treatment options and provide information on potential restrictions and exceptions for the use of certain therapies.

In addition, for the determination of the relevant question for the benefit assessment, criteria and patient characteristics have been specified to clearly distinguish relevant populations with respect to different treatment algorithms and disease prognoses within the therapeutic area. It is undisputed that in recent years some specialist fields have shown a certain dynamism in the development of medical knowledge. This does not only apply to further developments of treatment options, but also to categorisations of disease stages or characterisations by new biomarkers.

It is thus even more unfortunate that the IQWiG found out in a systematic analysis[9] that in some guidelines, the period between the evidence searches and the publication of the corresponding guidelines was between half a year and three years (6 to 44 months). In other cases some new active substances that underwent additional benefit assessment by the G-BA occurred were only included about six years later (8 to 78 months): For this analysis, indications were reviewed that were addressed in G-BA benefit assessment decisions from 1 January 2017 to 31 August 2018, and for which separate guidelines were available on the AWMF websites at the time of the decision (excluding orphan drug indications and conditional approvals).

In addition, it must be criticised that guidelines of adequate quality (S2k/S3) were only available for some 35 percent of the indications decided upon. The reviewed areas of application cannot be representative of the spectrum of guideline indications, since the selection only applies to indications for which pharmaceuticals have been developed recently. For several indications, pharmacotherapies are not yet available or no new pharmaceuticals have been developed yet that are subject to an evaluation during this period (e.g. Alzheimer's disease for which there is no G-BA decision about benefit assessment, but an S3 guideline). Thus, the above-mentioned proportion of 35 percent may well be under- or overestimated.

Nevertheless, e. g. for the indication of migraine, there is only one S1 guideline available from 2018 with an addendum from 2019 on monoclonal antibodies.[10] Yet this indication is of great importance for public health, because a relevant proportion of the population, namely some 15

percent of women and 6 percent of men, is affected by migraine in Germany.[11] In the meantime, decisions on the early benefit assessment have been made for the three monoclonal antibodies (erenumab, fremanezumab, galcanezumab)[12] used for migraine prophylaxis; in some cases even a reassessment based on new scientific findings.[13] During the consultations in this indication, especially on the status of existing therapies and their positioning and sequence in the therapeutic cascade of migraine prophylaxis, an S3 guideline that systematically addresses the available evidence on existing therapeutic options would have been helpful.

Medical guidelines provide the G-BA not only with information on ACT, but especially with information on relevant patient populations that can be distinguished from one another. One example is the current S3 guideline on the diagnosis, treatment, and follow-up of renal cell carcinoma.[14] Here, the „system therapy options according to risk profile in first-line therapy" are differentiated. The G-BA follows this classification of patient populations for the benefit assessment (see decision on cabozantinib in combination with nivolumab[15]) and follows the therapy recommendations in determining the appropriate comparator therapy for the most part (figure 2).

Different therapy regimens or disease progression prognoses addressed in guidelines usually provide guidance for the G-BA. The pharmaceutical company is then required to search for corresponding comparative data for these patient groups for the benefit assessment, if this is covered by the therapeutic area of the respective pharmaceutical. It is irrelevant whether these patients have been evaluated in the study. Consequently, the G-BA expects information on this issue in the IQWiG's benefit assessment. This may also mean that it is made transparent that no evidence is available for certain patient groups.

Looking at the individual guidelines, such as the aforementioned guideline on the diagnosis, therapy and follow-up of renal cell carcinoma, the G-BA is pleased to note from those decisions on new pharmaceuticals are increasingly mentioned in guidelines. However, the data contained in the documents published on the G-BA website are not used for the discussion of study results. For example, the study results table on study 1051 indicates that adverse events were not reported. However, in the pharmaceutical company's dossier, the dossier evaluation, and the decision on axitinib[16], the study results for this endpoint are shown (figure 3).

Furthermore, the G-BA's findings on additional benefit should be discussed to make the user of the guideline aware of the fact that the underlying research question of the guideline and the G-BA decision must be differentiated and that the different conclusions are precisely due to this fact. A G-BA decision on an additional benefit is not a medical guideline, but a population-based assessment of the available evidence to determine an additional benefit as compared to an appropriate comparative therapy that has been defined by the G-BA based on consistent methodological specifications. The specified comparative therapy does not always correspond to the comparator of the study and the patient population does not always correspond exactly to the entire study population. In addition, the patient relevance of the endpoints is centrally used for the assessment of additional benefit, which may differ from the endpoints that are considered relevant for the treatment decision from the attending physician's perspective.

In its decisions, the G-BA thus explains that the findings on the additional benefit do not restrict the treatment latitude required to fulfil the physician's treatment mandate. The fact that an additional benefit could not be proven does not mean that the pharmaceutical does not provide a

Comparison of the therapy recommendations of the guideline "Renal Cell Carcinoma" and patient group classification / zVT from the decision of the G-BA on cabozantinib + nivolumab

ACT of the G-BA (published: Cabozantinib + nivolumab)

Appropriate comparative treatment

1. Adult patients with non-pretreated advanced renal cell carcinoma with favourable risk profile (IMDC score 0)
   Appropriate comparative treatment for cabozantinib in combination with nivolumab:
   - Pembrolizumab in combination with axitinib
2. Adult patients with non-pre-treated advanced renal cell carcinoma with intermediate (IMDC score 1-2) or unfavourable risk profile (IMDC score ≥3) Appropriate comparative treatment for cabozantinib in combination with nivolumab:
   - Avelumab in combination with axitinib (only for patients with unfavourable risk profile) *or*
   - Nivolumab in combination with Ipilimumab *or*
   - Pembrolizumab in combination with axitinib

Status of information: December 2020

Guideline recommendation

Risk profile	Standard recommendation = strong recommendation	Option
low	Pembrolizumab + axitinib *Avelumab + axitinib	Bevazizumab + IFN Pazopanib Sunitinib Tivozanib
inter-mediate	Pembrolizumab + axitinib Ipilimumab + nivolumab *Avelumab + axitinib	Cabozantinib (B)** Sunitinib (B)** Pazopanib (B)** Tivozanib (B)** Bevazizumab + IFN (0)**
Unfavour-able	Pembrolizumab + axitinib Ipilimumab + nivolumab *Avelumab + axitinib	Cabozantinib (B)** Sunitinib (B)** Temsirolimus (0)** Pazopanib (0)**

Quelle: own presentation[14, 15]

Figure 2: Medical guidelines provide the G-BA not only with information on appropriate comparative therapies, but also with information on relevant patient populations that should be differentiated, e. g. on the example of renal cell carcinoma.

benefit. Nevertheless, it is worth taking a closer look at the conclusions of the G-BA, because the decision may be based on even more findings than the guideline.

5. Conclusions

The independent funding of guidelines – as stipulated in the DVG – should be fully supported. Guideline authors must systematically prepare and evaluate the evidence for a large number of different questions in an indication and derive appropriate recommendations for action from it. Without adequate support, the requirements of the various users cannot be reliably met in the required quality.

From the G-BA's point of view, the following points should be achieved in particular through the promotion of guideline development:

- minimise involvement of people with conflicts of interest;
- improve systematics and completeness in evidence research and processing;
- ensure that the guidelines are up to date; and
- transparent considerations for recommendations for action in cases with incomplete or uncertain knowledge.

The difficulty is to explicitly express uncertainties and heterogeneous outcomes besides clearly quantifiable, measurable outcomes. In this context, limitations of guidelines

Comparison of the results of study 1051 from the guideline "Renal cell carcinoma", p. 101 and from the decision of the G-BA on Axitinib

Results of the AGILE 1051 study			
Benefit/Aspects of harm	**Axitinib**	**Sorafenib**	**p-Wert**
Response rates (ORR=CR + PR)	32 %	15 %	
Drop-out rates*	3 %	2 %	
Dose reduction	25 %	43 %	
Side effects grade 3 + 4	NR	NR	

AE-asociated, AE = adverse events; ORR = objective response rate; CR = complete regression; PR = partial regression; SD = stable disease; NR = not reported; NA = not applicable

End point	**Intervention group** Axitinib		**Control group** Sorafenib		Intervention vs control
	N	Median survival time (weeks) [95% CI] *Patients wit event n (%)*	N	Median survival time (weeks) [95 % CI] *Patients with event n (%)*	Hazard ratio [95 % CI] p-value
Severe AEs (CTCAE grade 3 or 4)					
AXIS (2. DS 01.11.2011)	126	4,6 [3.0; 7.5] *86 (68.3)*	123	2,8 [1.1; 6.0] *87 (70.7)*	0,84 [0.62; 1.13] *0.250*
A4061051/2L (DS 31.10.2011)	68	6,5 [4.1; 9.3] *40 (58.8)*	35	6,5 [0,9; 13,8] *22 (62.9)*	0.87 [0.52; 1.46] *0.600*

Quelle: Own presentation[14, 16]

Figure 3: From the G-BA's point of view, it is positive if guidelines indicate the G-BA's decision-making on new pharmaceuticals.

must be acknowledged, because the heterogeneous mix of sometimes conflicting values as represented by different interest groups, or the society as a whole cannot be addressed by guidelines. This can only be remedied with a high-quality, evidence-based synthesis of knowledge reflecting the current state of knowledge.

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Guidelines – recognising what matters

Professor Ina B. Kopp | AWMF-Institute for Medical Knowledge Management

The COVID 19 pandemic, at the latest, makes it clear that health policy and individual health care must be based on the findings of scientific medicine. The professional societies provide guidelines with concrete recommendations for action. To make the reliability of guidelines transparent, the Association of the Scientific Medical Societies in Germany (AWMF) has established a quality-assured guideline registry. But guidelines must be updated to the current state of knowledge more quickly and provided more individually to meet individual information needs. For this purpose, the AWMF pursues a comprehensive concept for the digitisation of guidelines. This requires structural, independent funding.

All around the world, medical guidelines are considered to be of great importance for both the development of quality and the management of healthcare. Guidelines are defined as „systematically developed statements that reflect the current state of knowledge and facilitate decision-making by physicians, other healthcare professionals, and patients for appropriate care in specific clinical situations".[1] They „contain recommendations for the enhancement of the quality of care" and „are based on a systematic review of the evidence and weighing of the benefits and harms of alternative approaches."[2] Accordingly, guidelines are an essential instrument for quality development in healthcare – but they must meet specific quality requirements and be reliable and trustworthy.

In 1994, the then Expert Council for Concerted Action in Health Care asked the Association of Scientific Medical Societies (AWMF) to begin collecting recommendations on preventive, diagnostic, and therapeutic measures – under the premise of „self-responsibility, subsidiarity, and solidarity" – that could be used as a basis for quality assurance once consensus had been reached with other physician organisations.[3]

In contrast to the development in other countries – where national guideline programmes were either centrally directed or not directed at all – the Council of Experts reaffirmed the ownership of medical science in its 1995 special report.[4]

This request has both led to an enormous commitment of the scientific medical societies to provide guidelines for healthcare quality assurance and establish a high-quality guideline registry of the AWMF.[5, 6] Essential here is the transparency regarding the extent of the systematic development process, which is reviewed by the AWMF and can be seen at a glance (see figure 1).

Reliability of guidelines: Transparency about the extent of systematic development of a guideline in the AWMF registry ("S classes")

S 3	**Evidence and consensus-based guideline**	Representative panel, systematic search, selection, evaluation of literature, structured consensus building
S 2e	**Evidence-based guideline**	Systematic search, selection, assessment of the literature
S 2k	**Consensus-based guideline**	Representative panel, structured consensus building
S 1	**Recommendations for action by expert groups**	Consensus building in an informal process
Requirement for all classes: Statement of interests and handling of conflicts of interest		

SYSTEMATIC

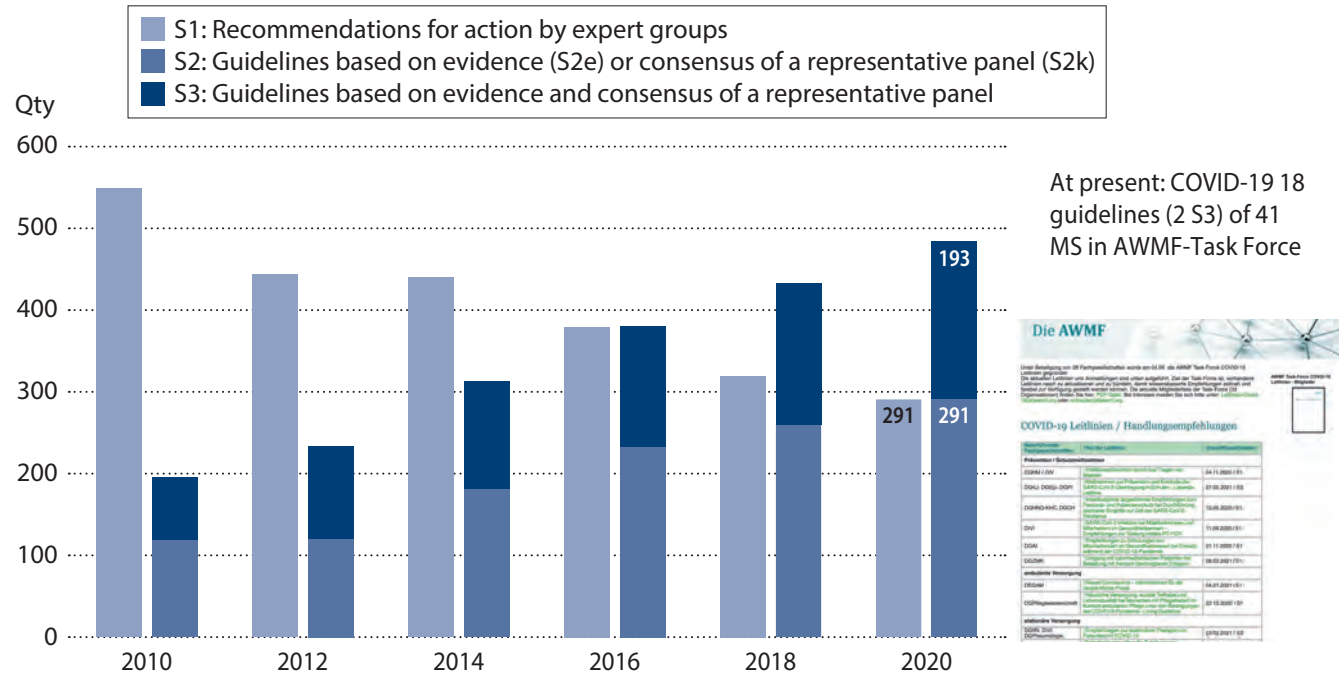
Source: AWMF

Figure 1: The AWMF quality-assured guideline registry is characterised by its transparency regarding the extent to which the development process is systematic. This is reviewed by the AWMF and can be seen at a glance.

Professor Ina Kopp *has headed the Institute for Medical Knowledge Management of the Association of the Scientific Medical Societies (AWMF-IMWi) since its foundation in 2009. She has been Vice Chair of the AWMF Standing Commission on Guidelines since 2004. From 2012 to 2021, she was a member of the Board of Directors of the Guidelines International Network (GIN), while also serving both as Vice President and President. She was and is active in numerous independent bodies as an advisor/member (Scientific Advisory Board of the Institute for Quality Assurance and Transparency in Health Care (IQTiG), Scientific Advisory Board of the German Agency for Quality in Medicine (ÄZQ), SCIANA-the Health Leaders Network). In her scientific work and publications, she focusses on the development, implementation and evaluation of clinical guidelines and health services research. Her clinical background is in surgery and emergency medicine.*

Development of the AWMF guideline registry: commitment of the medical societies

Cross-sectional analysis as of 1 November of a year



Source: Monika Nothacker, Cathleen Muche-Borowski, Ina B. Kopp
Institute for Medical Knowledge Management of the Association of the Scientific Medical Societies (AWMF-IMWi), Marburg, Germany

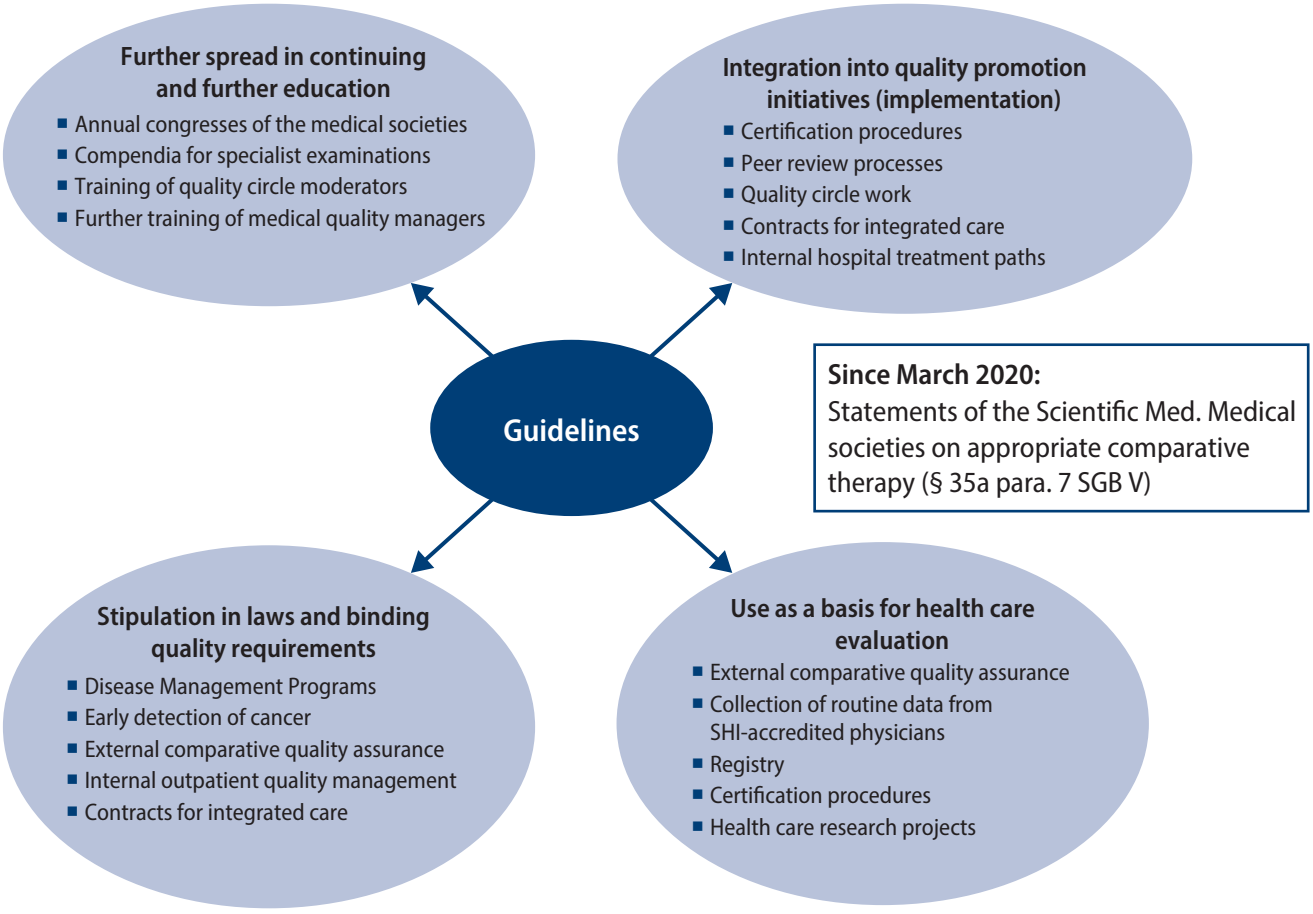
Figure 2: The development of the AWMF guideline registry demonstrates an increasing commitment by professional societies to provide high-quality S3 class guidelines for relevant health problems.

The development of the AWMF guideline registry demonstrates an increasing commitment by professional societies to provide high-quality S3 class guidelines on relevant health problems. Against the background of the COVID 19 pandemic, the professional societies reacted promptly and – at the request of the Ministry of Health in 2020 – developed 18 guidelines within only a few months, which are subject to continuous updating according to the evolving state of knowledge (see figure 2).

The commitment of the professional societies regarding the development of guidelines and comprehensible quality assurance by the AWMF have contributed to the fact that guidelines from the quality-assured registry of the AWMF are perceived as a trustworthy source of knowledge and widely used in the German healthcare system (see figure 3).[7, 8]

AWMF registry guidelines serve as a trustworthy knowledge base for:

Importance of guidelines in the German healthcare system

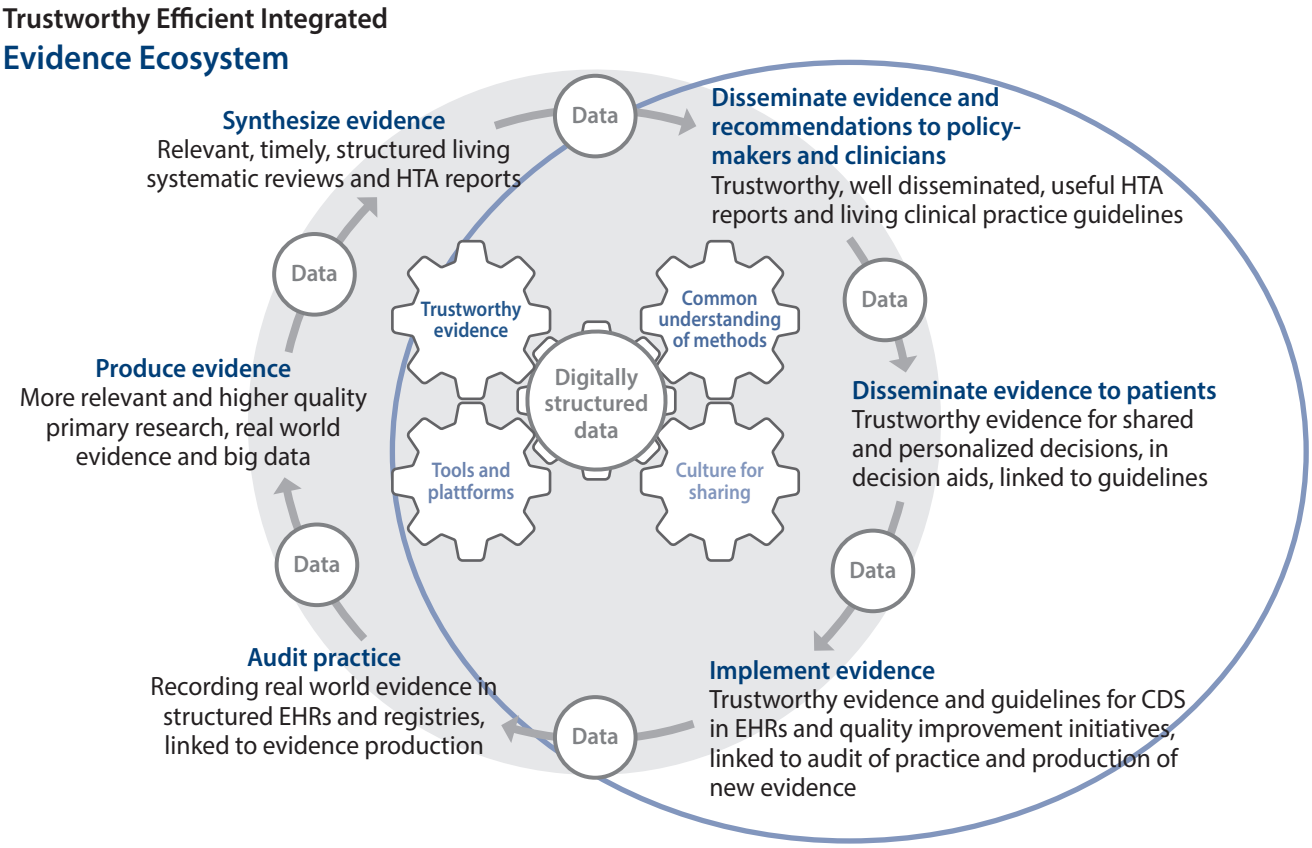


Source: AWMF

Guidelines from the quality-assured registry of the AWMF are perceived as a reliable and trustworthy source of knowledge and widely used in the German healthcare system.

- Participatory decision making in the context of individual healthcare at the „point of care".
- Provision of health information for citizens
- Medical education and training (e.g. stipulation in the National, Competency-based Learning Objectives Catalogue (NKLM), and in the Catalogue of Examination Questions of the Institute for Medical and Pharmaceutical Examination Questions (IMPP)

International perspective: digitisation of guideline knowledge as part of the evidence ecosystem



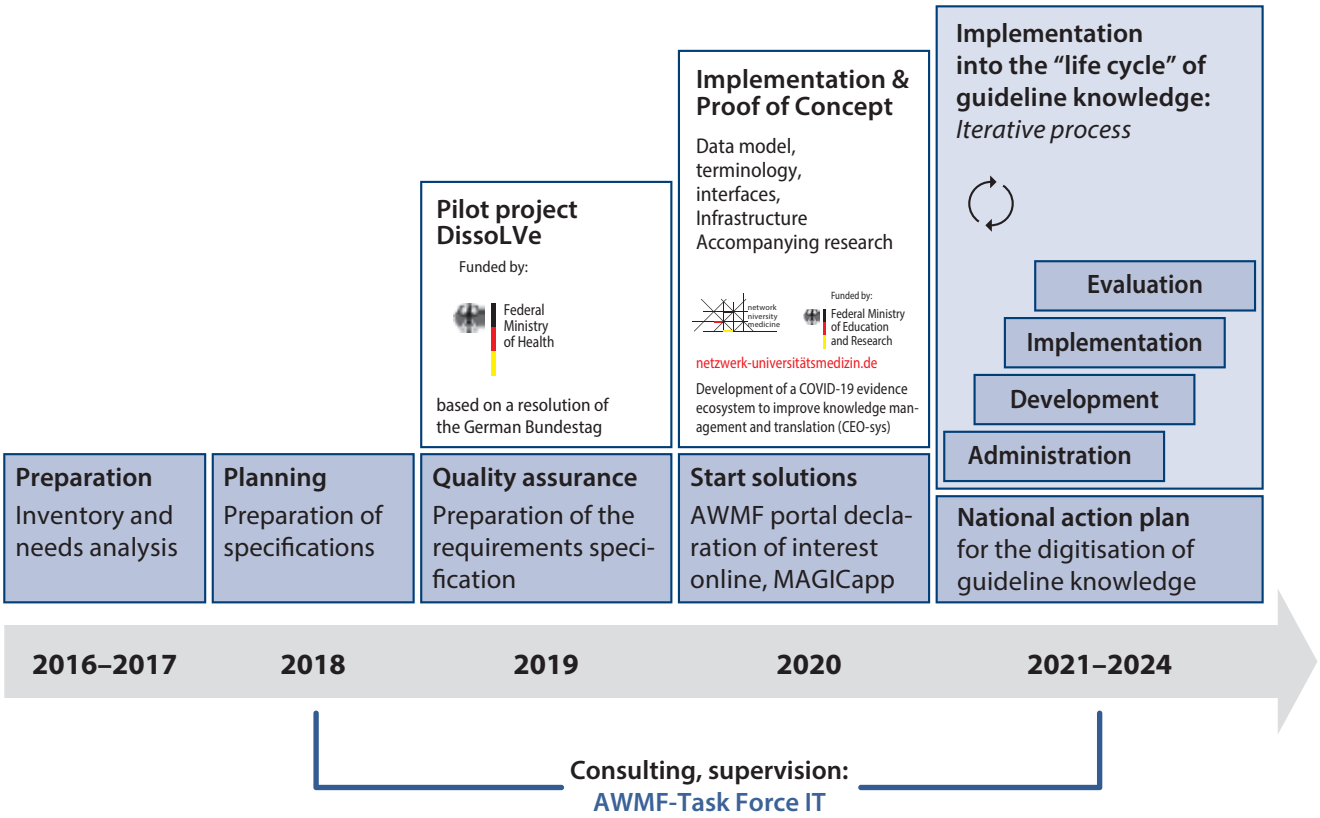
Source: AWMF; (Reproduced with permission from MAGIC Evidence Ecosystem Foundation [www.magicevidence.org].)

Figure 4: As guideline knowledge often does not arrive where it is needed, it must be digitised to ensure its widespread use. For this purpose, the AWMF pursues a comprehensive strategy.

- Social and criminal law assessment procedures
- Quality initiatives - especially for the certification of centres and external comparative quality assurance according to SGB V
- Identification of „knowledge gaps“ and research needs – especially for the benefit assessment of medical technologies and healthcare research
- Evidence-based policy advice – for example, in the context of the Covid 19 pandemic.

However, at the moment, guideline knowledge is not getting to where it is needed. To achieve a better penetration, guideline knowledge needs to be digitised. To this end, the

Digitisation of guideline knowledge: Overall concept of the AWMF



Source: AWMF

Figure 5: The transfer of guideline knowledge and AWMF guideline registry into a digital format requires independent, structural funding.

AWMF pursues a comprehensive strategy that follows the international consensus of establishing a digital, trusted evidence ecosystem (see figure 4).[8]

Against this background, the AWMF has identified the requirements for the digitisation of guideline knowledge through research projects.[9,10]

Conclusion

The transfer of both guideline knowledge and the AWMF guideline registry into a digital format are essential.

The main objectives include:

1. To promote the development and updating of guidelines by using digital tools and applications, including AI solutions;

2. To improving availability of quality-assured knowledge from guidelines to enhance healthcare (e.g. via the BMG health portal, the electronic patient record (ePA), decision support systems in clinics and practices);

3. To improve the transfer of current guideline knowledge in medical education and training;

4. To empower patients and citizens to participate in medical decisions;

5. To identify and specify research needs.

The implementation requires independent, structural funding.

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Guidelines – which quality criteria exist?

Corinna Schaefer M.A. | German Agency for Quality in Medicine, Berlin

There are numerous standards on quality criteria for clinical practice guidelines (CPGs). It is international consensus that strict methodology, balanced group composition, and CoI management (conflict of interest) are the major quality characteristics of CPGs. The Central Guidelines Registry in Germany with its associated quality management ensure a high level of quality. Compliance with quality criteria has an influence on the trust in and implementability of CPGs; thus, they are not merely methodological ends in themselves, but can ultimately improve patient care. However, especially in case of the desirable continuous updating, a disproportion may arise between the use of resources on the one hand and the relevance to patient care and knowledge gain on the other hand.

Background

Not all guidelines are the same. Anyone who works with guidelines knows: There are major differences in the safety and reliability of guidelines and their recommendations. In particular, if there are several – possibly even contradictory – guidelines for a single indication, it is important to recognise which ones can be relied on and where caution is required. By the way: several contradictory guidelines on one indication represent a barrier to implementation.[1]

The term „guideline" is not protected. Nevertheless, the Association of the Scientific Medical Societies (AWMF), which has established a central registry for medical guidelines in Germany, has a well-established classification system categorising guidelines according to key features of the development process.[2]

By independently and critically reviewing each guideline before including it into the registry, the AWMF ensures that the criteria for the respective quality level have been met. This provides users an initial orientation regarding the reliability and robustness of the recommendations made. The criteria of the AWMF registry reflects the international consensus (see next section). With the systematic assessment of all CPGs included in the German CPG Registry, the AWMF has implemented a form of nationwide quality assurance providing one of the international leading systematic approaches. Thus, guidelines can be used with a high level of quality transparency in Germany.

Quality criteria for guidelines – international development

The quality discussion has been going on for decades and there is a broad international consensus on what constitutes a good guideline. This has already been discussed in Germany since the 1990s (e.g.[3]) and a broad international

debate has developed. In the following section, some important papers and publications will be highlighted that reflect an internationally developing consensus on the quality criteria of guidelines. A distinction should be made between papers outlining methodological requirements, assessment tools for CPGs, and checklists for the report quality of CPGs.

In particular, the methodological aspects of evidence-based practice as well as critical weighing of options were highlighted by the Institute of Medicine of the National Academies in 2011 in its standard work „Clinical Practice Guidelines We Can Trust": „Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[4]

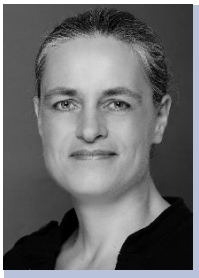
The Guidelines International Network (G-I-N) stipulated the first standards for the international guideline community in a methods paper[5] and presented a quality checklist for guideline developers together with McMaster University.[6] Shortly thereafter, G-I-N also established criteria for transparent handling and management of conflicts of interest.[7]

The AGREE consortium also outlined various criteria for the systematic assessment of CPGs; the second edition of the AGREE tool (AGREE II) presents the international standard for the systematic assessment of CPGs.[8] The AWMF regulations mentioned at the beginning, which are binding for Germany, are also based on it. Moreover, the RIGHT Statement outlines the requirements for the report quality of CPGs.[9]

Broad international consensus

Even if the many publications are not completely consistent due to various objectives, and even if we observe a development over time – especially towards stricter methodological requirements – a set of quality criteria can be derived that can be found in all of them representing a kind of international consensus about the characteristics of a reliable guideline. Here, both people making recommendations as well as the process by which these recommendations were developed play a role (figure 2).

For Germany, these quality criteria have been stipulated in the AWMF regulations. Guidelines that have been included in the registry with S3 classification mainly fulfil the requirements outlined above. Publications of the Institute for Quality and Efficiency in Health Care (IQWiG) confirm that it is not only an assumption that these criteria are in fact fulfilled: For the continuous update of the DMP Require-



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Classification of guidelines in Germany

Type	Characteristics of development	Effort	Methodological legitimacy	Political legitimacy
Recommendations for action by experts **(S1)**	Panel selects no systematic development	low	low	normative low
Consensus-based LL **(S2k)**	Panel representative formalised consensus process	medium	low	normative high
Evidence-based LL **(S2e)**	Panel selects evidence-based	high	high	normative low
Evidence and consensus-based LL (S3)	**Panel representative evidence-based formalised consensus process**	**very high**	**high**	**normative high**

Source: own illustration

Figure 1: The Association of the Scientific Medical Societies in Germany (AWMF) has established a classification system that categorises CPGs according to key features of the development process.

ments Guideline[10], the IQWiG is regularly commissioned to systematically research and evaluate national and international guidelines on DMP indications. This shows that German S3 guidelines, in particular the National Health Care Guidelines (Nationale Versorgungsleitlinien, NVL), range among the best in international comparison (figure 3).

Particularly against the background of the increasing methodological demands on guidelines and the associated need for resources, the question arises as to whether these quality criteria are methodological ends in themselves or whether they make a difference to patient care. In the following section, a few criteria will be outlined as examples to demonstrate their importance for the robustness and applicability of a guideline.

Quality criteria of guidelines – International overview

- Balanced composition of the guideline group
- Management of conflicts of interest
- Evidence-based and outcome-orientation
- Formal consensus procedure
- Transparent recommendation rationale
- Timeliness / update procedure

Source: own illustration

Figure 2: Quality criteria can be derived from many publications representing a kind of international consensus on the characteristics of a reliable guideline.

Composition of the guideline group

Representatives of guideline groups tend to rate interventions which they also provide in their practice or institution, respectively, as more important and better evidenced in terms of benefit than representatives who do not provide this particular intervention. This fact sounds relatively

Compare quality assessment of guidelines

liminary report (preliminary assessment) V20-05 Version 1.0
DMP Heart failure 19.07.2021

A3.3 Assessment of the methodological quality of guidelines

The assessment of the methodological quality of the guidelines according to AGREE II is shown in table 26 below.

Table 26: Result of the methodological assessment

AGREE II domain / Guideline	Standardised domain values[a] (ranking)[b]						Number of domains with domain score >30%
	Domain 2: Interest groups		Domain 3: methodological accuracy		Domain 6: editorial independence		
AAFP 2017	**17%**	**(11)**	**26%**	**(12)**	**4%**	**(12)**	0
ACC 2017	31%	(5.5)	70%	(4)	71%	(2.5)	3
AND 2017	22%	(8.5)	63%	(5)	13%	(11)	1
CCS 2017	31%	(5.5)	40%	(7)	21%	(9)	2
CCS 2020 heart	31%	(5.5)	39%	(8)	21%	(9)	2
CCS 2020 position	31%	(5.5)	56%	(6)	21%	(9)	2
DGPR 2020	**97%**	**(1)**	74%	(2)	71%	(2.5)	3
ESC 2018	**17%**	**(11)**	35%	(9)	50%	(5.5)	2
ESC 2020	**17%**	**(11)**	33%	(10)	50%	(5.5)	2
NHF 2018	22%	(8.5)	32%	(11)	33%	(7)	2
NICE 2018	53%	(3)	72%	(3)	58%	(4)	3
NVL 2019	89%	(2)	**84%**	**(1)**	**92%**	**(1)**	3
MW (SD)	38% (28)		52% (20)		42% (27)		

Bold highlighted: lowest and highest values of a domain.
a) standardised domain value = (achieved score - minimum score) / (maximum score - minimum score). The value ranges from 0 to 100%.
b) In case of equal standardised domain value, middle ranks were assigned
AGREE: Appraisal of Guidelines for Research & Evaluation; MV: mean value; SD: Standard deviation

Basis for the design of DMPs

Source: IQWiG, 2021: https://www.iqwig.de/download/v20-05_dmp-herzinsuffizienz_vorbericht_v1-0.pdf

Figure 3: Assessments of the methodological quality of CPGs have repeatedly shown that German S3 CPGs, especially the National Health Care Guidelines, are among the best in international comparison.

obvious, but has also been demonstrated empirically.[11] Therefore, for an unbiased evaluation of individual interventions in a guideline, a committee is required that reflects as many different perspectives as possible.

Therefore, the AWMF rulebook for all S2k and S3 guidelines stipulates that all user groups of the guideline as well as patients are involved from the beginning in the development process.[2] Compliance with this rule has been shown to influence the quality of a guideline: A multidisciplinary panel will probably assess the benefit of interventions more critically and more in line with the evidence, as shown e.g. by comparing the National Health Care Guideline on Heart Failure[12] with the guideline of the European Society of Cardiology[13]: The indications for both pharmaceuticals (e.g. ivabradine, sacubitril/valsartan) and interventional procedures (CRT for atrial fibrillation, ICD in primary prevention) are more cautious in the NVL than in the ESC guideline, justified in particular by the available evidence and its limited methodological reliability.[14]

One RCT shows: If patients are involved in the development of the guideline process as equal members, efficacy will be assessed more strongly based on patient-relevant endpoints.[15] According to a study within a German guideline group, patients sometimes consider different aspects of harm to be relevant.[16]

In summary: A guideline group composed of as many important disciplines and professional groups as possible, as well as patient representatives, will help minimise professional bias and increase the relevance of a guideline for the target population. This is not a theoretically plausible assumption but has been demonstrated in various studies.

Management of conflicts of interest

Direct financial interests, as well as indirect, academic, or other interests, present a risk for a biased interpretation of evidence.[17] The AWMF regulations include an algorithm for the structured assessment of and management of conflicts of interest. All guideline group members disclose their interests in writing and third parties will assess the severity of these conflicts of interest. In case of minor conflicts of interest, mandate holders in guideline groups should not take on leadership roles; in the case of moderate conflicts of interest, they should abstain from voting; in case of major conflicts of interest, they are excluded from the consultations.[2]

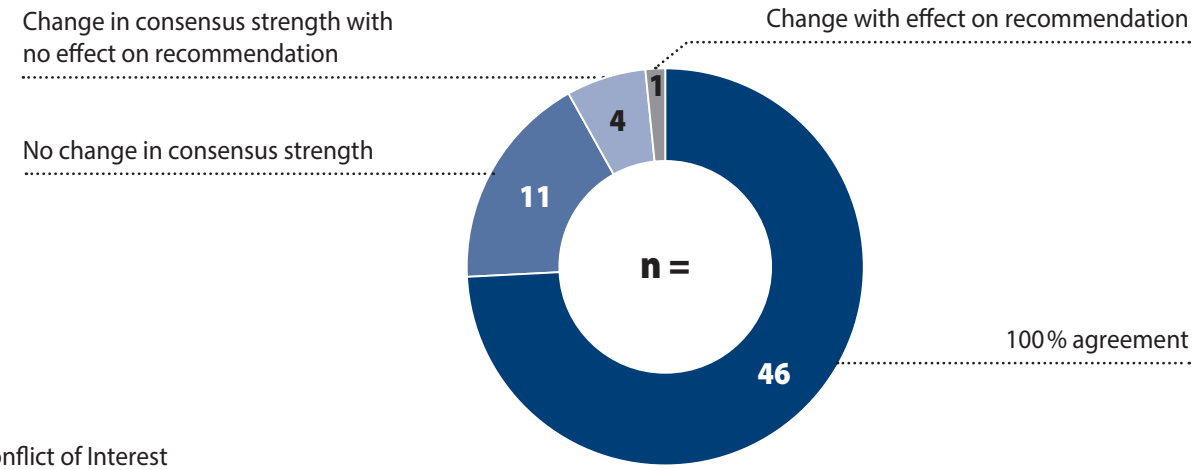
Since 2018, a systematic survey was conducted within the scope of the National Health Care Guidelines Program to determine whether abstentions due to conflicts of interest influence voting outcomes[18]: If abstentions due to conflicts of interest had been specified in votes, blinded double voting was conducted: Initially, all elected officials voted regardless of whether there was a conflict of interest. The result was recorded but remained secret unless 100 percent approval was achieved (a result that could not be changed by abstention). In a second vote, officials with a conflict of interest abstained, and only then were the results announced. For a total of five guidelines, there were 62 votes with relevant conflicts of interest (figure 4).

In three-quarters of these votes, a consensus of 100 percent was reached, so a double vote was not necessary. In 15 recommendations (24 percent), abstentions did not affect the recommendation. In only one recommendation (1.6 percent) abstentions resulted in relevant consequences for the recommendation. Other protective factors, such as a strong, multidisciplinary panel and a rigorous, robust methodology, might also have contributed to the lack of influence of conflicts of interest on the guidelines. Therefore, it is questionable, whether this can be transferred to guidelines with less rigorous methodology.

Beyond all specific influences on guideline content, it can be ascertained: A transparent management of conflicts

Evaluations of double voting due to CoI abstentions

62 blinded double votes for abstention due to moderate CoI



CoI: Conflict of Interest

Source: Schüler S, Schaefer C. Conflict of interest management – does it make a difference? (2021). G-I-N conference Abstract book. Guidelines International Network, 2021: 63.

Figure 4: Within the scope of the NVL programme, since 2018, it has been systematically evaluated by means of blinded double voting whether abstentions due to conflicts of interest change voting results.

of interest contributes significantly to the public perception and credibility of guidelines. The platform leitlinienwatch.de which is operated by Transparency Deutschland, MEZIS and Neurology First, evaluates German CPGs according to how strictly they deal with conflicts of interest. Of a total of 154 guidelines that have been evaluated to date, only 21 percent were rated well, 46 percent had moderate deficiencies, and 32 percent serious deficiencies (www.leitlinienwatch.de).

Evidence-based and transparent justification of recommendations

For S2e and S3 guidelines, the AWMF rules and regulations require a systematic identification of evidence, assessment of benefit based on priori prioritised outcomes, and clear link of the derived recommendations to the underlying evidence.[2] In particular, the other reasons that play a role in the formulation of recommendations in addition to the benefit-harm ratio and the reliability of the evidence (e.g. clinical experience, ethical considerations, alternative actions, and priority) should also be presented in a transparent manner.

Thus, every reader can understand why the guideline group made the recommendation in the way it did. This form of transparent justification promotes credibility and user confidence in a guideline, as the evaluation of the National Health Care Guidelines Program has shown[1]: In the qualitative part of the study, the 45 physicians surveyed indicated that they found NVLs credible and reliable, particu-

larly because of their transparency and methodology:

„It is really scientifically based. That is what makes it so comprehensive. Therefore, it is credible and transparent. They always justify their conclusion properly. That is what makes it a bit of a read – it's a scientific read, not some funny pseudo-specialised book." (Quote from interview with a general practitioner). This quote also highlights the dilemma of transparency: guideline texts are getting longer - with too much text, in turn, can make guidelines more difficult to use, which is another finding of the NVL evaluation. Therefore, it is important to develop new presentation formats and prepare the CPGs in several „levels" with different levels of information.

In the associated quantitative online survey of 667 people, 90 percent of those who knew the NVL said they would recommend the National Health Care Guidelines to others.

It is thus plausible that people who trust a guideline are more likely to implement the respective recommendations. A transparent evidence base and recommendation rationale can therefore promote the implementation of guidelines, as the evaluation of the NVL program shows.

Outlook: Timeliness

Guidelines that are not perceived as up to date have a lower level of acceptance.[1] According to the AWMF rulebook, a guideline must be updated at least every five years.[2] The basis for this rule is a study that revealed that more than half of the evaluated guideline recommendations were no longer current after five years.[19] The concept of continuous updating, so-called „living guidelines", is gaining in importance. According to AWMF regulations, guidelines must be reviewed annually.

Increasingly, guidelines tend to review the need for updating at close intervals. However, if this is done in the same quality that it is required for S3 guidelines in Germany, this is associated with a considerable expenditure of resources. This is due to the fact that all development steps are required at short intervals, but sometimes only for a small number of recommendations, for example all coordination processes between the involved organisations or a public consultation. At the same time, a look at German guidelines updated in the „living" format so far shows which type of recommendations trigger updates particularly often: In most cases, evidence on new pharmaceuticals triggers the update.

In NVLs, a systematic survey is conducted at the beginning of each new update round to determine how the guideline group assesses patient care and which goals the guideline is intended to achieve. Regularly, and across all NVL indications, the groups cite the following goals as priorities:

- Strengthening the importance of non-drug and lifestyle-related measures
- Strengthening communication, agreement on individualised treatment goals, and decision-making according to the bio-psycho-social model
- Promoting adherence and self-management.

On the other hand, guideline groups often realise – particularly with new evidence on pharmaceutical measures – that they often demonstrate the efficacy of an active ingredient in general. But the studies are usually not suitable for therapy guidance, because it remains unclear how pharmaceuticals will fit into the current context of care with the options for action that are already available. For example, regarding the integration of dupilumab into biologics therapy stage 5, the authors of the NVL Asthma note:

„Because of the positive effects on the rate of severe exacerbations and the potential to reduce OCS, the guideline group sees an option for a therapy trial with dupilumab in stage 5 for the patient group that has narrowly been defi-

ned in recommendation 4-36 with failed asthma control after inhalation therapy has been exhausted. At the same time, they observed that in the studies no comparison was made to the other monoclonal antibodies – which have been approved for some time – a fact, which makes a comparative assessment difficult".[20]

This suggests that „living" formats require a lot of resources to produce a topicality that on the one hand, does not necessarily relate to the most urgent challenges of patient care thus presenting little potential for improvement and, on the other hand, cannot be direct drivers for care providers, because relevant questions have not been answered. It is difficult to judge whether this expenditure of resources is really justified in terms of improving patient care.

After all, even though the impact on patient care may seem small, close update intervals may help to increase users' confidence in a guideline. As mentioned above, the lack of timeliness is one of the barriers to guideline use.[1] However, whether „living guidelines" can actually be implemented more effectively has not yet been investigated.

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Clinical guidelines – a comment from the industry's perspective

Dr Julia Wagle | Medical Director of Roche Pharma AG

We appreciate scientifically based, practice-oriented recommendations for action that represent the current state of science. They provide physicians with relevant data for the best possible patient care. A physician's therapeutic decision for or against the prescription of a certain pharmaceutical should be based primarily on the guidelines of the professional societies, not on the assessment of the additional benefit by the G-BA. AMNOG is a pricing instrument that was not designed for healthcare management. Therapeutic freedom and provision of the best possible information for the attending physician, e.g. by means of up-to-date guidelines and appropriate classification of G-BA decisions by the professional societies, represent the basis for optimal patient care.

Guidelines are essential for optimal patient care

They provide orientation for both physicians and patients within the scope of decision-making and options for action. They provide physicians with relevant data in a condensed form for the best possible patient care within the framework of individual therapeutic freedom. For us as a pharmaceutical company, national guidelines are relevant because they reflect the treatment standard in Germany. They help us to identify clinically relevant comparators in the planning phase of studies and develop new therapies according to clinical need. Guidelines provide an external independent classification of our and other therapies in the course of treatment.

It is thus desirable that high-quality guidelines, if possible S3 guidelines, are available in all (major) therapeutic areas. However, due to the rapidly advancing medical developments, these guidelines sometimes become outdated because of new scientific findings and thus lose some of their clinical relevance. We are also facing this challenge in the design of novel studies.

And digitisation will increasingly provide clear support here. From our point of view, the concept of „living guidelines", as we saw during the COVID pandemic for the first time, can become a sustainable model for the future.

The determination of an adequate appropriate comparator therapy (ACT) in the context of benefit assessment requires current guidelines

As part of our own research, we reviewed the current use of guidelines in the context of the early benefit assessment. In the indications that are relevant to us, predominantly oncology and neurology, a total of 40 benefit assessment procedures were initiated from March to Decem-

ber 2020. In 30 of the 40 procedures, German S3 guidelines were identified as the basis for the determination of the ACT in the literature search of the Federal Joint Committee (figure 1).

14 of the 30 available guidelines had last been updated no longer than two years ago. 13 of the guidelines were last updated two to five years ago, three guidelines even more than five years. Of course, the necessity of an update clearly depends on the indication area and the respective current developments. Overall, however, at least 50 percent of our research was based on a fairly up to date German S3 guideline. Of course, this may be different in other indications.

From our point of view, the following questions are important and should be wisely weighed against each other in the search within the scope of the benefit assessment:

- How up to date is the guideline?
- How much is the guideline related to the German treatment context?
- How valuable is the guideline?

From our point of view, the increased involvement of professional societies (e.g. in the determination of the ACT) in benefit assessment procedures and early consultations was a particularly important step to improve decision making. Within the scope of our research, the professional society/ies has/have so far been involved in the question of the ACT in only 12 of the 40 procedures.

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Application of existing guidelines in benefit assessment procedures

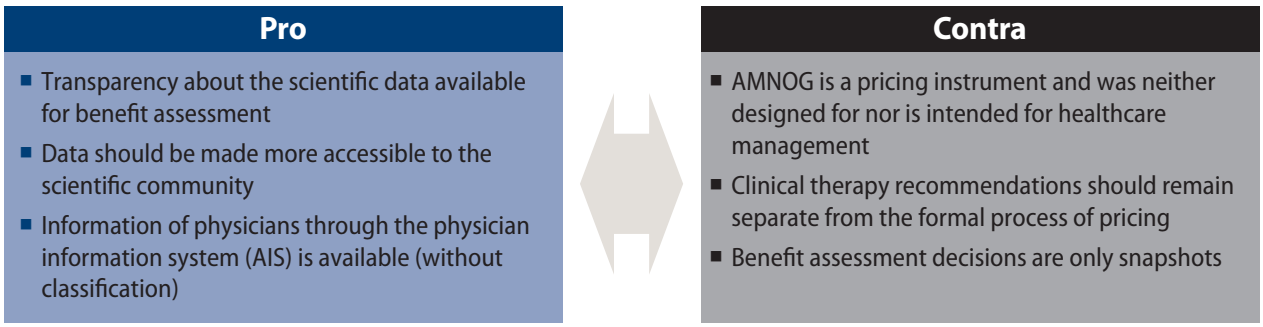
Mini-research:

- Evaluation of procedures in indications relevant to Roche, primarily oncology and neurology
- 40 benefit assessment procedures
- March 2020 to December 2020
- Involvement of professional societies in the question of the appropriate comparative therapy: 12/40
- German S3 guideline available (G-BA literature search): 30/40
  Last update
  - Less than 2 years ago: 14
  - 3 to 5 years ago: 13
  - More than 5 years ago: 3

Source: Roche Pharma AG, internal evaluation

Figure 1: In about half of the evaluated benefit assessment procedures, a fairly current German S3 guideline was available.

Should benefit assessment decisions be included in guidelines?



Source: Own presentation, presentation on the occasion of the Autumn Meeting 2021 of the Interdisciplinary Platform

Figure 2: There are divergent views on the question of including benefit assessment decisions in guidelines. From the industry's point of view, AMNOG is primarily a pricing instrument which is not intended for healthcare management.

G-BA decisions on benefit assessment procedures should be considered in the guidelines

In general, we appreciate the incorporation of the G-BA decisions on benefit assessment procedures into the guidelines. However, a physician's therapeutic decision for or against the prescription of a certain pharmaceutical should be based primarily on the guidelines of the professional societies, not on the assessment of the additional benefit by the G-BA (figure 2).

AMNOG is a pricing instrument and was neither designed for nor is intended for healthcare management. Clinical therapy recommendations should remain separate from the formal process of price negotiation. Therapies can fail the methodological requirements in AMNOG and still be the treatment of choice in the guidelines. Evaluations of two pharmaceuticals based on equivalent evidence may differ depending on the timing of the evaluation. These are only snapshots; requirements for ACT may change over time because of new therapeutic options.

On the other hand, the introduction of the AMNOG system has provided a huge amount of detailed scientific data for the first time. In our view, this data should be made available to physicians and the scientific community to a greater extent and adequately processed for this purpose. We view the current presentation of G-BA decisions in the physician information system with a critical eye due to the lack of adequate classification and link to current guidelines and thus welcome the ongoing initiatives in this regard.

Therapeutic freedom and the best possible information for physicians, e.g. by means of up-to-date guidelines and appropriate classification of G-BA decisions by the professional societies, represent the basis for optimal patient care. Only in this way can optimal therapeutic decisions be made.

Clinical guidelines: Their role from benefit assessment to patient care

Dr Klaus Schlüter | Medical Director, MSD Sharp & Dohme GmbH

The importance of guidelines in medical care varies considerably across specialty groups. The increasing evidence-based nature of guidelines has led to increased acceptance and relevance in clinical care in recent years. Especially in oncology, guidelines are crucial for the treatment of patients. Apart from their relevance for clinical care, guidelines play a decisive role from the perspective of a pharmaceutical company in the planning of clinical study programmes. Moreover, they are also of particular importance for the consideration of appropriate comparative therapies in the benefit assessment process of the Federal Joint Committee.

Guidelines in healthcare

The importance of guidelines in medical care varies considerably across specialty groups. In a publication about information needs and behaviour of general practitioners, Lang and Zok demonstrated that the quality judgement about relevant information sources is generally higher than the actual utilisation value. In general, English publications and evidence databases are not considered very much. Guidelines from medical societies and national healthcare guidelines, although rated well by the majority, are also used by some 30 percent of the respondents only (see figure 1).[1]

In a survey among general practitioners about their guideline orientation, 71 percent said they preferred to rely on their own practice rather than on guidelines. At the same time, however, 80 percent of the respondents were also convinced that guidelines provide a structured approach to diagnosis and therapy. Easy applicability, legal certainty, descriptive design, and consideration in the schedule of fee were cited as critical success factors for the acceptance of guidelines.[2] The increasing evidence-based nature of guidelines has led to increased acceptance and relevance in clinical care in recent years.[3] Especially in oncology, guidelines are crucial for the treatment of patients. Seufferlein et al. demonstrated that more than 90 percent of all tumour entities are now covered by guidelines (see figure 2).[4]

Guidelines and study design

Apart from their relevance for clinical care, guidelines play a decisive role from the perspective of a pharmaceutical company in the planning of clinical study programmes. Study designs - especially for phase 3 studies – are guided by national and international guidelines. These are also of

Importance of guidelines in (general) medical care

Use and evaluation of various sources of information
Proportions "very frequently" and "frequently" or "very well" and "well" in percent; n = 1,003

	Use (very) frequently	Evaluation (very) good
Impersonal, classical sources		
… German-language specialist publications	63.8	78.0
… other guidelines from medical societies	34.8	65.2
… National health care guidelines (NVL)	28.4	61.9
… special medical articles in publication media	26.4	16.5
… information from the health industry	17.7	17.7
… information from statutory health insurances	16.3	14.9
… international English-language publications	14.6	49.1
… information from pharmacies	8.6	19.4
Personal sources		
… continuing medical education	77.2	80.2
… medical quality circles	47.9	73.2
… information from medical colleagues	44.7	56.6
… information from pharmaceutical representatives	36.2	18.9
… national/international congresses	18.6	67.0
Interactive media		
… physician platforms with interactive components	28.2	36.3
… evidence databases	12.1	54.1

The quality assessment of relevant information sources is usually higher than the actual utilisation value. English publications and evidence databases are rarely used.

Source: Britta Lang, Klaus Zok. „Informationsbedürfnisse und -verhalten von Hausärzten" (Information needs and behaviour of primary care physicians); WIdOmonitor 1/2017.

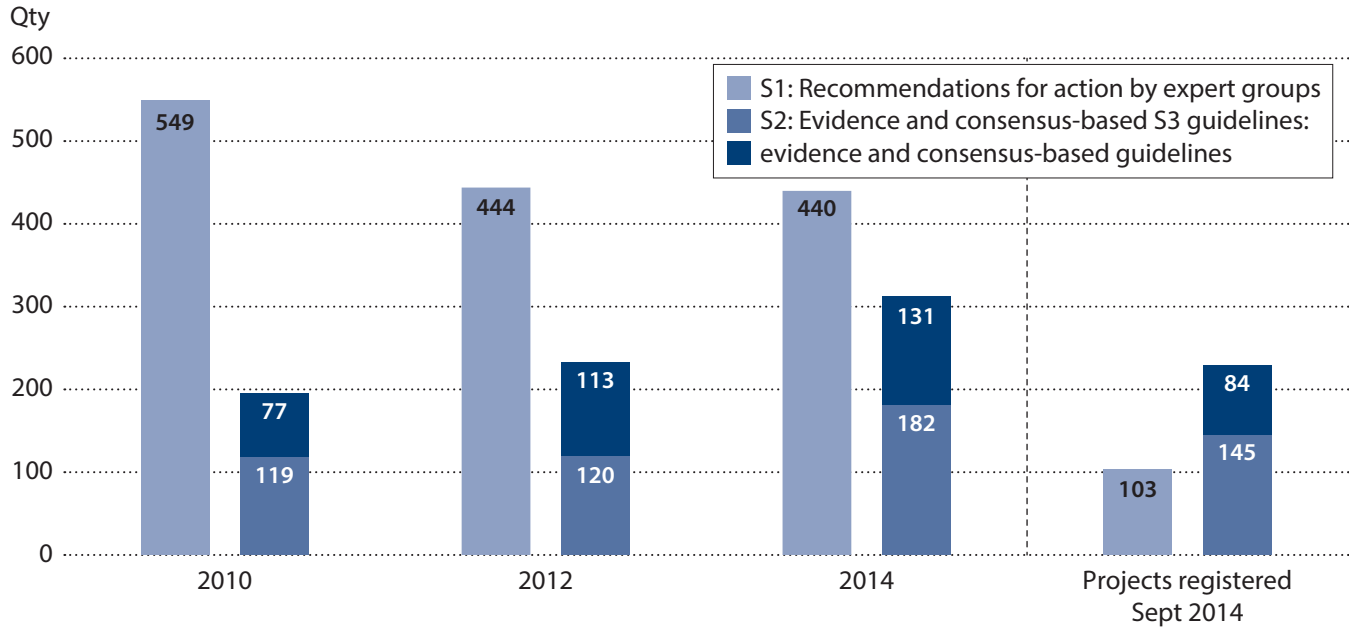
Figure 1: The importance of guidelines in physician care varies depending on the type of source: national health care guidelines are well rated, but little used. The same is true for English publications.

particular importance regarding the consideration of appropriate comparative therapies in the benefit assessment process of the Federal Joint Committee.

Developments in recent years have raised critical issues for the pharmaceutical industry in this context:

- Does a change in a guideline imply a change in an appropriate comparative therapy in the benefit assessment process by the Federal Joint Committee?
- Do guidelines reflect the actual medical care situation and thus the actual costs of statutory health insurance?

ncreasing evidence-based nature of guidelines increases acceptance and relevance



ource: Monika Nothacker, Cathleen Muche-Borowski, Ina B. Kopp
Institute for Medical Knowledge Management of the Association of the Scientific Medical Societies (AWMF-IMWi), Marburg, Germany

Figure 2: In recent years, the increasing evidence-based nature of guidelines has led to increased acceptance and relevance in clinical care – especially in oncology.

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- How are new indications and new clinical pictures addressed?
- And finally: How significant are future European guidelines for the AMNOG process, especially against the background of a European HTA process?

These open questions should be discussed and answered by all stakeholders to further enhance acceptance of guidelines on the one hand and ensure a reliable and comprehensible benefit assessment process on the other hand.

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Guidelines: evidence-based, up to date, relevant – challenges using the example of oncology

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Guidelines are evidence-based recommendations for action. They build a bridge between external evidence – which is currently rapidly increasing in many areas – and the individual patient situation. In medicine, and especially in oncology, guidelines cover the entire range of prevention, early detection, diagnostics, and therapy. In contrast to regulations or directives, guidelines serve as decision-making aids. They evaluate the available evidence in terms of different patient-relevant outcomes and derive corresponding recommendations. In the clinical setting, guidelines provide a corridor for joint decision making of physicians and patients. Particular challenges for guidelines in oncology include quality and transparency of production, timeliness, and ease of access. In recent years, guidelines have become an essential element of quality assurance in healthcare.

History of medical guidelines in Germany

Germany, there have long been approaches for treatment recommendations taking cost-effectiveness into account.[1] However, guidelines in their current structure have only emerged some 30 years ago.[2, 3] The need increased with the number of clinical trials. Independent analyses became necessary because of different designs and quality of the standard-setting studies, including divergent results for similar indications. The standardised evaluation of the results should result in up to date guidelines for diagnostics and treatment. In Germany, the Council of Experts for Concerted Action in Health Care had addressed the development of guidelines, directives, and recommendations in 1995 and in 1996, the German Medical Association defined these different forms of instructions for action as follows:[4]

Directives: rules of action and omission issued by an institution that only leave limited scope for the individual physician.

Guidelines: systematically developed decision-making aids about appropriate approaches granting the individual physician a certain degree of individual choice and „corridors of action" which can be derogated from in justified individual cases.

Recommendations: aim at guiding physicians and the general public to areas requiring modification and attention.

Memorandum: serves at providing comprehensive information and clarification; they shall also be useful to differentiate between the current state of knowledge and obsolete knowledge

In 1995, the German Medical Association and the National Association of Statutory Health Insurance Physicians founded the Central Office of the German Medical Professi-

on for Quality Assurance in Medicine; since 2003, it is known as the German Agency for Quality in Medicine (ÄZQ). Since 1995, the coordination and publication of guidelines is one of the central tasks of the Association of the Scientific Medical Societies (AWMF). The AWMF defined a quality hierarchy for German-language guidelines from S1, S2k, S2e to S3.[5] This classification has been implemented in Germany but has not yet become established worldwide

Legal framework

The recommendation or non-recommendation of a certain pharmaceutical in the National Health Care Guideline on Pain Therapy also resulted in a judicial clarification of the legal framework of guidelines in 2011 after a pharmaceutical company had filed a lawsuit.[6] The developers of the guideline were sued, in this case Association of the Scientific Medical Societies in Germany (AWMF), German Medical Association, and National Association of Statutory Health Insurance Physicians (KBV). Cologne District Court dismissed the case on 30 November 2011 stating: „If the procedure is performed based on a statement – like in this case – the distinction whether it is a factual claim or expression of opinion will be of particular importance. (...) It is accepted by the case-law, that any expression of opinion associated with the publication of such tests does not represent an illegal infringement, if the assessment and evaluation were performed neutrally, objectively, expertly, and thoroughly using reasonable evaluation methods."

The judgement was affirmed in the second instance by the Higher Regional Court on 6 November 2012: „In general, AWMF, BÄK, and KBV as developers and editors are responsible for the content. The same applies for medical associations who develop and publish guidelines under their own responsibility. (...) These statements are evaluations and expressions of opinion." An appeal against the decision was not allowed.

Tasks

The aim of guidelines is to improve medical care by communicating knowledge based on the current state of scientific knowledge. Healthcare is not provided in a binary world in which there are only the opposing sides, such as „effective" vs „ineffective" or „appropriate" vs „inappropriate". In an increasingly complex data situation, guidelines provide the corridor within which evidence-based care is provided to patients. Figure 1 shows an example of the complexity of decision-making in oncology.

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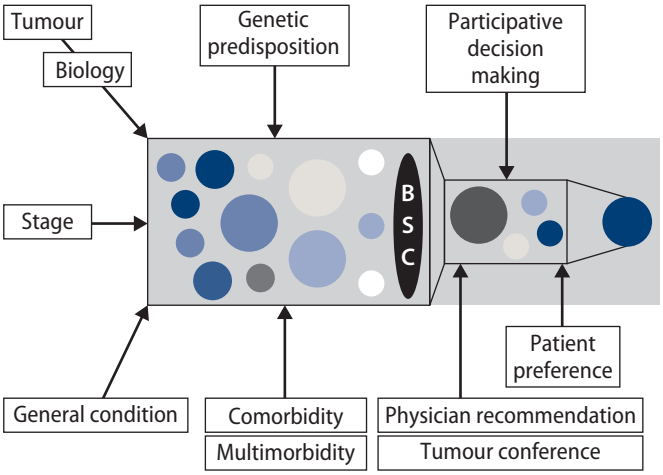
Elements of decision making in oncology



The task field of guidelines is shown in grey

Source: Prof. Bernhard Wörmann

Figure 1: Healthcare is not provided place in a binary world – guidelines show corridors within which evidence-based medical care takes place.

Challenges

The concept of guideline development, presentation and dissemination needs to be reviewed and adapted on a regular basis.

Effort

The effort required for the preparation of guidelines is also high in Germany. One example: 60 mandate holders and 30 experts were involved in the development of the multidisciplinary S3 guideline „Supportive therapy in oncological patients". These guidelines have been developed within the framework of the guideline programme on oncology by the Association of the Scientific Medical Societies (AWMF) with a budget of up to 300,000 to 400,000 Euros. This funding does not include the volunteer hours of the mandate holders and experts of the participating professional societies.

Publication bias

Guidelines are based on published data from randomised clinical trials (RCTs). The preferential publication of positive study results[7] and – especially in case of new pharmaceuticals – the lack of long-term results is associated with a certain imbalance. Moreover, many publications are based on industry approval studies. These are primarily aimed at obtaining approval and do not necessarily reflect the issues in clinical practice. The data for „excluded patients" (older age, comorbidities) is often poor. This bias is particularly evident in pharmaceutical trials.

Methodological quality

The basis of every guideline is evidence-based medicine (EBM). In the early years, the criteria for the evaluation of data and representation of consensus building were inconsistent which also led to contradictory statements in different guidelines on the same topic.[8] In recent years, consistent international assessment criteria for guidelines have been developed.[9, 10] They are not always identical with criteria from evaluation procedures with other intentions.[11]

Timeliness

Guidelines are only updated at relatively long intervals because of the huge organisational and financial effort involved. The usual interval is five years. In specialised fields and in indications with relatively little innovation, such a period is acceptable. But in research-intensive and innovative fields, such as oncology, five years is far too long. Some guidelines are no longer up to date in all their recommendations when they are published.

Guideline of the Mamma Commission of the Working Group Gynaecological Oncology (AGO

Anal carcinoma	Adult soft tissue sarcoma	Actinic keratosis and squamous cell carcinoma of the skin
Chronic lymphocytic leukaemia (CLL)	Endometrial carcinoma	Follicular lymphoma
Urinary bladder carcinoma	Skin cancer prevention	HCC and biliary carcinoma
Testicular tumours	Hodgkin's lymphoma	Colorectal carcinoma
Complementary medicine	Laryngeal carcinoma	Lung carcinoma
Gastric carcinoma	Breast cancer	Melanoma
Multiple myeloma	Oral cavity carcinoma	Renal cell carcinoma
Ovarian cancer	Oesophageal cancer	Palliative care
Pancreatic cancer	Penile carcinoma	Prostate cancer
Psycho-oncology	Supportive therapy	Cervical carcinoma
Cervical cancer prevention		

Source: https://www.ago-online.de/leitlinien-empfehlungen/leitlinien-empfehlungen/kommission-mamma

Figure 2: Since 2008, 31 guidelines have been published within the framework of the German Guideline Programme in Oncology (GGPO).

Oncology guidelines in Germany Oncology guideline programme

Since 2008, the Guideline Programme in Oncology has been funded in Germany. With the German Guideline Programme in Oncology (GGPO), the AWMF, the German Cancer Society and German Cancer Aid had set the goal of jointly promoting and supporting the development, updating and use of scientifically based and practicable guidelines in oncology.[12, 13] Figure 2 shows that 31 guidelines have been published so far. The validity of the guidelines is

Oncology guideline programme as of 12/2021

	Oxford		
	LoE	GR	AGO
■ GnRHa + fulvestrant + CDK4/61	2b	B	++
■ GnRHa + AI + ribociclib	1b	B	++
■ GnRHa + AI + palbociclib/abemaciclib	3b[a]/5	C	+
■ GnRHa + tamoxifen + palbociclib/abemaciclib	2b	B	+/–
■ GnRHa + tamoxifen	1a	A	+
■ Tamoxifen	2b	B	+/–
■ GnRHa + AI (first + second line)	2b	B	+
■ GnRHa + fulvestrant	1b	B	+
■ Aromatase inhibitors without OFS	3	D	––

GnRHa plus fulvestrant plus palbociclib

1. Turner N et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med 2015; 373:209-219
2. Loibl S, et al. Palbociclib Combined with Fulvestrant in Premenopausal Women with Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results. Oncologist. 2017;22(9):1028-1038.
3. Finn RS et al: Treatment effect of palbociclib plus endocrine therapy by prognostic and intrinsic subtype and biomarker analysis in patients with bone-only disease: a joint analysis of PALOMA-2 and PALOMA-3 clinical trials Breast Cancer Res Treat 2020 Nov;184(1):23-35. doi: 10.1007/s10549-020-05782-4. Epub 2020 Aug 11.

GnRHa plus AI plus palbociclib

1. Layman RM et al. Comparative effectiveness of palbociclib plus letrozole vs. letrozole for metastatic breast cancer in US-real world clinical practises, ESMO 2019, #329P

GnRHa plus AI/Tamoxifen plus ribociclib

1. Tripathy D et al. First-line ribociclib vs placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized phase III MONALEESA- 7 trial. SABCS 2017, GS-2

Source: Guideline programme in oncology by AWMF, DKG and DKH: http://www.awmf.org/leitlinien/leitlinienprogramme/ol-programm.html

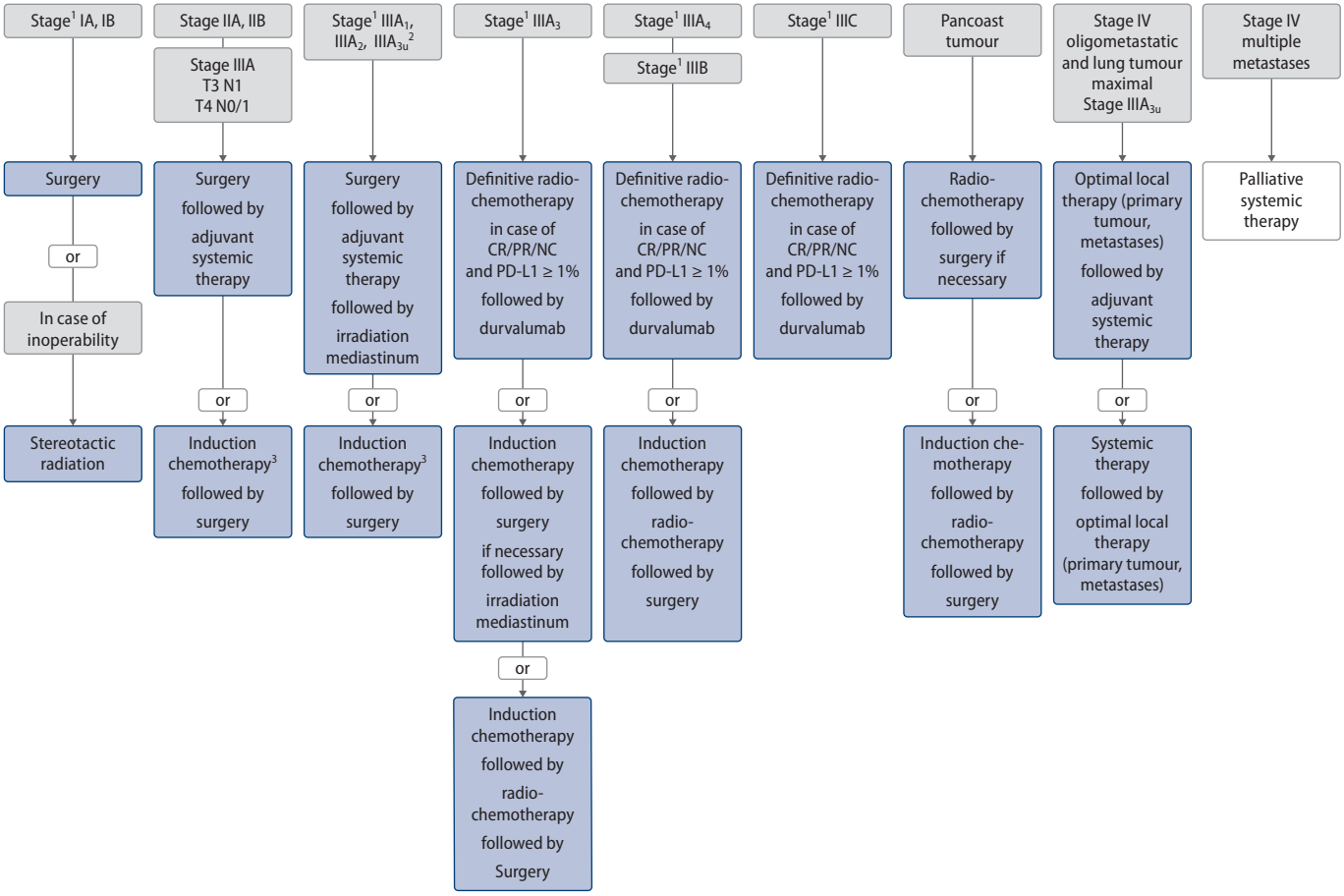
Figure 3: Guideline programme of the Working Group on Gynaecological Oncology – using a current example of recommendations for breast cancer with schematic representation of level of evidence and strength of recommendation.

usually five years. A further development with the aim of ensuring that recommendations are up to date is the concept of the „Living Guideline“ (any dialectical opposition is not intended). Depending on the situation, earlier and modular updates are possible.

Working Group Gynaecological Oncology

An outstanding example of organ-related guidelines with high quality and rapid updating is the guideline programme of the Working Group Gynaecological Oncology (AGO).[14] The AGO is an independent association of the Ger-

Algorithm from ONKOPEDIA for the therapy of non-small cell lung cancer, as of 7/2021



Source: Griesinger F et al.: Non-small cell lung cancer (NSCLC). Guidelines of DGHO, OeGHO, SGMO and SGH+SSH, status April 2021 https://www.dgho-onkopedia.de/de/onkopedia/leitlinien/lungenkarzinom-nicht-kleinzellig-nsclc

Figure 4: With ONKOPEDIA, the DGHO has established a dedicated portal for haematology and oncology. The information is available for everyone – here the example of the therapy algorithm for small cell lung carcinoma.

man Society of Gynaecology and Obstetrics (DGGG) and the German Cancer Society. Since the end of the 1990s, guidelines have been drawn up for this specialist field. Institutional commissions publish regular updates of these evidence-based guidelines, consented at a separate guideline conference, e. g. annually for breast cancer. Figure 3 shows a current example of recommendations in breast cancer with a schematic representation of the level of evi-

dence, classification according to GRADE, and strength of recommendation according to the AGO methodology.

ONKOPEDIA

In 2010, the DGHO has established the ONKOPEDIA portal for haematology and oncology. It is supported by the scientific medical societies of the German-speaking countries.[15] ONKOPEDIA is ‚Open Access', i. e. the information is available to everyone, including patients and their relatives. It is characterised by the uniform structure of all guidelines, the limitation to 15 to 40 pages and the integration of algorithms (see figure 4).

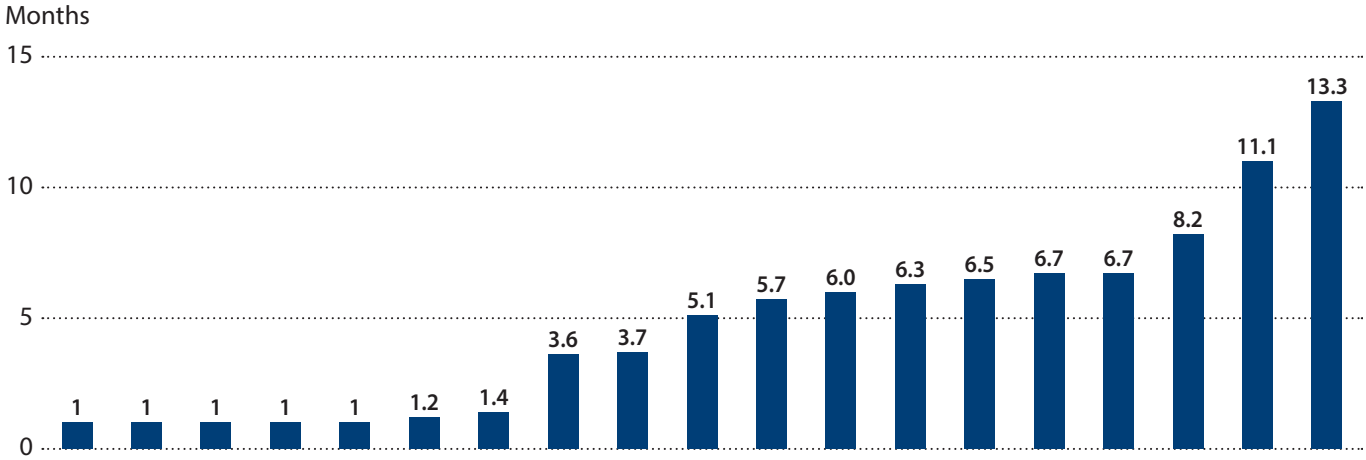
So far, more than 70 guidelines have been created in ONKOPEDIA. The condensed structure allows for faster elaboration. Professor Eva Lengfelder has evaluated the chronological sequence of guidelines on haematological neoplasms (see figure 5).[17]

The time span is 5.8 months on average, with a median of 6 months.

Physician/Hospital Information Systems (AIS/HIS)

The next step for guidelines will be the integration into physician/hospital information systems (AIS/HIS). Presumably, this will be done in several steps. In a first step, they could be integrated into document guidance systems. Initially, uncommented guidelines in pdf format could be used. However, interaction with local structures is crucial for the acceptance and implementation of the guidelines.

Time from call to completion of guidelines on haematologic neoplasms in ONKOPEDIA



Source: Lengfelder E: ONKOPEDIA – Guidelines and other functions. Joint Annual Meeting of the German, Austrian and Swiss Societies of Haematology and Medical Oncology (Hybrid Congress),1-4 October 2021, Abstract 517, 2021. Oncol Res Treat 44:1-335, 2021. DOI: 10.1159/000518417

Figure 5: The uniform and condensed structure of the guidelines – currently more than 70 – enables their rapid development. For the guidelines on haematological neoplasms, it takes an average of 5.8 months.

This could be achieved by means of commenting on adopted guidelines, so to speak in the form of a conversion to in-house guidelines (personal notice of Professor Ansgar Weltermann, Linz).

It remains to be seen whether the future integration of guidelines into expert decision-making systems which is expected by many stakeholders will be successful in the near future. Such an implementation will lead to an increased requirement for the uniformity of the structure, the precision of the description of recommendations for action and the processes of updating. The functionality of such systems will largely depend on whether the above mentioned „corridor" can be provided or whether this will turn out as an electronic corset.

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Guidelines in cardiology – European collaboration

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Guidelines are a key instrument to ensure a nationwide, evidence-based, up to date and high-quality medical care. In cardiology, the integration of national and European guideline work is very advanced. Every year, the ESC publishes about four to five guidelines based on a clearly defined and structured process. In case of evidence gaps or different national approval procedures or national care situations will often result in differences in international guidelines. For the guideline on atrial fibrillation published in 2016, the ESC made use of the Cochrane Collaboration for the first time to conduct systematic reviews. Nowadays, an expert for meta-analyses participates in every guideline group as an author. A good and close cooperation of different stakeholder groups and disciplinary and national boundaries contribute significantly to the successful ESC guideline work. This is highly relevant, especially against the background of the increasing Europeanisation of the benefit assessment process. Due to this ongoing quality advancement, the German Society of Cardiology adopts the ESC guidelines commenting them in German.

High relevance of European guidelines also in the national context

Guidelines are a central tool for the implementation of comprehensive, evidence-based, up-to-date, and high-quality medical care in everyday clinical practice. They change and shape the respective clinical practice. From scientific publications and use in a wide range of training and education panels to practical pocket checklists, guidelines are important aids for physicians, nurses, and patients. In addition, high-quality guidelines play a key role for clinical and practice leaders, regulatory experts, health policy experts, as well as for modern health technology assessment.

After a careful review of the processes and content, the German Society of Cardiology decided to adopt the guidelines of the European Society of Cardiology (ESC) several years ago. This decision was taken on the basis of the high quality of the recommendations and both transparency and quality of the processes involved in the development of the guideline. These are available in different formats in German. At the same time, comments by the DGK about ESC guidelines in German on a timely basis provide valuable hints for the adaptation to the German healthcare system. The guideline website of the German Society of Cardiology[1] provides an overview of cardiology guidelines (see figure 1).

The bold guidelines in the graphic represent the ESC guidelines. Moreover, the „comments" basically refer to the German comments and translation of other ESC guidelines. It is thus obvious that in cardiology the integration of national, international and European guideline work is very advanced. European guidelines set the direction and national guidelines follow them (see figure 1).

Preparation of ESC guidelines: a well-established and structured process

The ESC homepage contains detailed information on the governing policies and procedures for the European ESC clinical practice guidelines.[2] The ESC publishes approximately four to five guidelines every year. The Committee for Practice Guidelines (CPG), consisting of some 25 experts, plays a key role in the preparation of these guidelines.[3] Guideline topics are proposed by the CPG and subsequently approved by the ESC leadership.

In addition, the CPG excludes any potential discrepancies between the different guidelines. The guidelines will be updated as soon as new evidence becomes available. In a next step, the CPG nominates a qualified chairperson to select and lead the guideline task force members in consultation with the ESC subgroups involved and according to the established processes and schedules. The CPG also nominates a Review Coordinator who selects the team of reviewers in consultation with the ESC Constituent Bodies and coordinates several rounds of peer review in the various stages of guideline development.

Some 25 experts and representatives of all national cardiology societies of the ESC member countries comments on the review process in two rounds. The entire process – from the appointment of the chair of the task force to the initial publication of the guideline – takes approximately two years.[2] The national implementation of the ESC guideline in Germany also includes comments by DGK experts.

Once the guideline has been completed, it is implemented via various channels and formats. This process is also highly professionalised, and CPG and the guideline task force receive operational support. Scientific publications at the ESC congress and in the ESC journals begin with the dissemination, followed by various educational activities such as websites, CME questions, webinars, and educational courses of the European Heart

Heart House (EHH) at international and national levels. Based on the support of the respective national cardiology societies, European guidelines are translated into the respective national language, localised accordingly, and used in national publications and initiatives.

Reasons for differences between guidelines

Because of the considerable progress and new evidence for treatment options for atrial fibrillation (AF), a comparison of the corresponding European (ESC), US (ACCF/AHA/HRS), and Canadian guidelines (CCS) was per-

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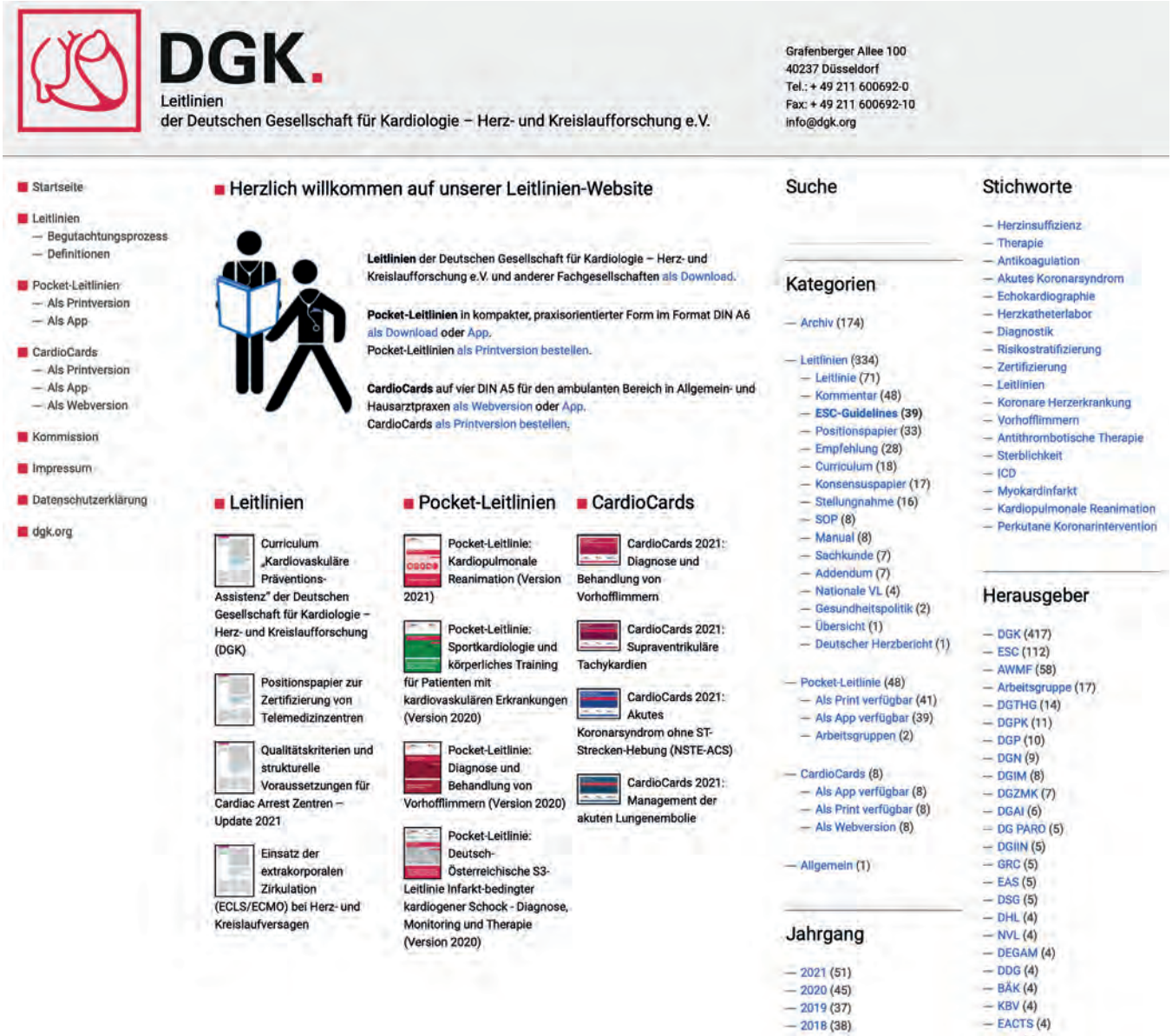
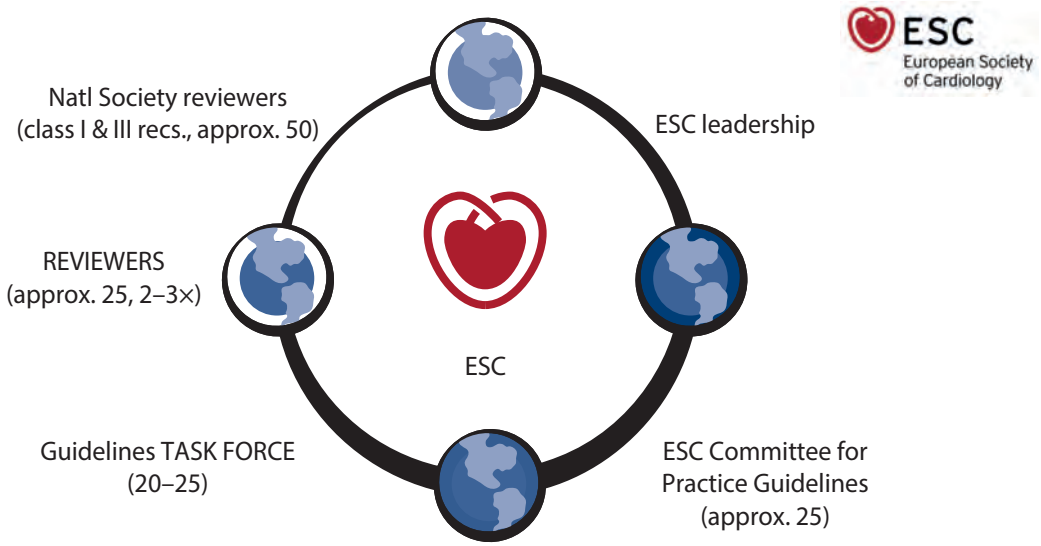
Presentation of the guidelines on the website of the German Society of Cardiology



Source: https://leitlinien.dgk.org (accessed on 12 December 2021)

Figure 1: Overview of cardiology guidelines on the website of the German Society of Cardiology.

Implementation of ESC guidelines



Source: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines (accessed on 12 December 2021)

Figure 2: ESC guidelines are prepared according to a structured process. This takes about two years from the appointment of the task force chair to the initial publication of the guideline.

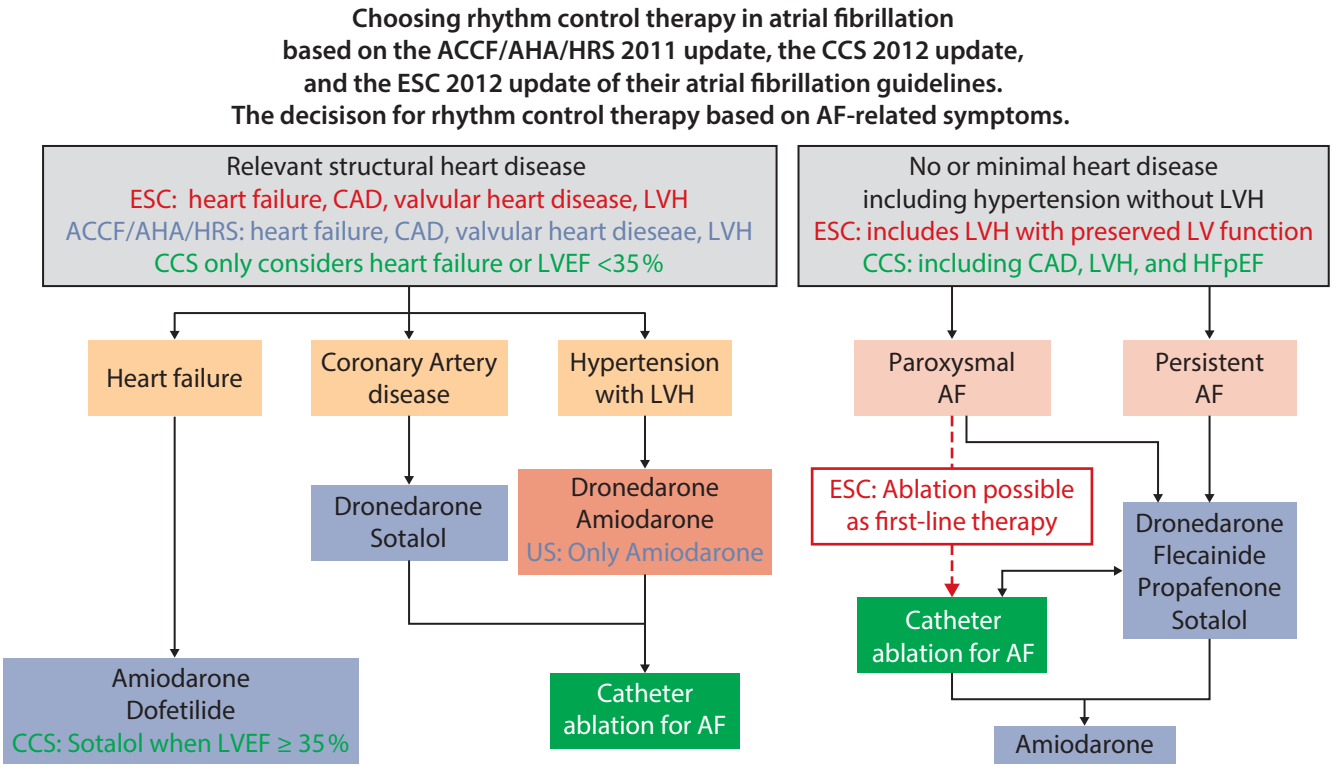
formed in 2012/2013. In areas with sufficient evidence, such as recommendations for anticoagulation or rhythm-maintaining therapy, this comparison showed mostly identical or strongly overlapping recommendations of the three guidelines. However, in the upper part of the graphic differences between the US and European recommendations for „facultative" (class II) recommendations were particularly evident (red boxes, figure 3).

While the US guidelines were designed as a mere update of previous recommendations, new guidelines were developed by the ESC task force differentiating by patient category or pre-existing condition (heart failure, coronary artery disease, hypertension with left ventricular hypertrophy, paroxysmal atrial fibrillation, persistent atrial fibrillation) to better reflect the newly available evidence (see figure 3).

From the authors' perspective, the differences between the reviewed guidelines could be attributed to three main reasons:[4]

- Recommendations for action based on expert consensus in case of evidence gaps;
- Different regulatory context or approval status;
- Different actual medical care situation (culture of medical practice).

Comparison of the European (ESC), US (ACCF/AHA/HRS) and Canadian (CCS) guidelines on atrial fibrillation



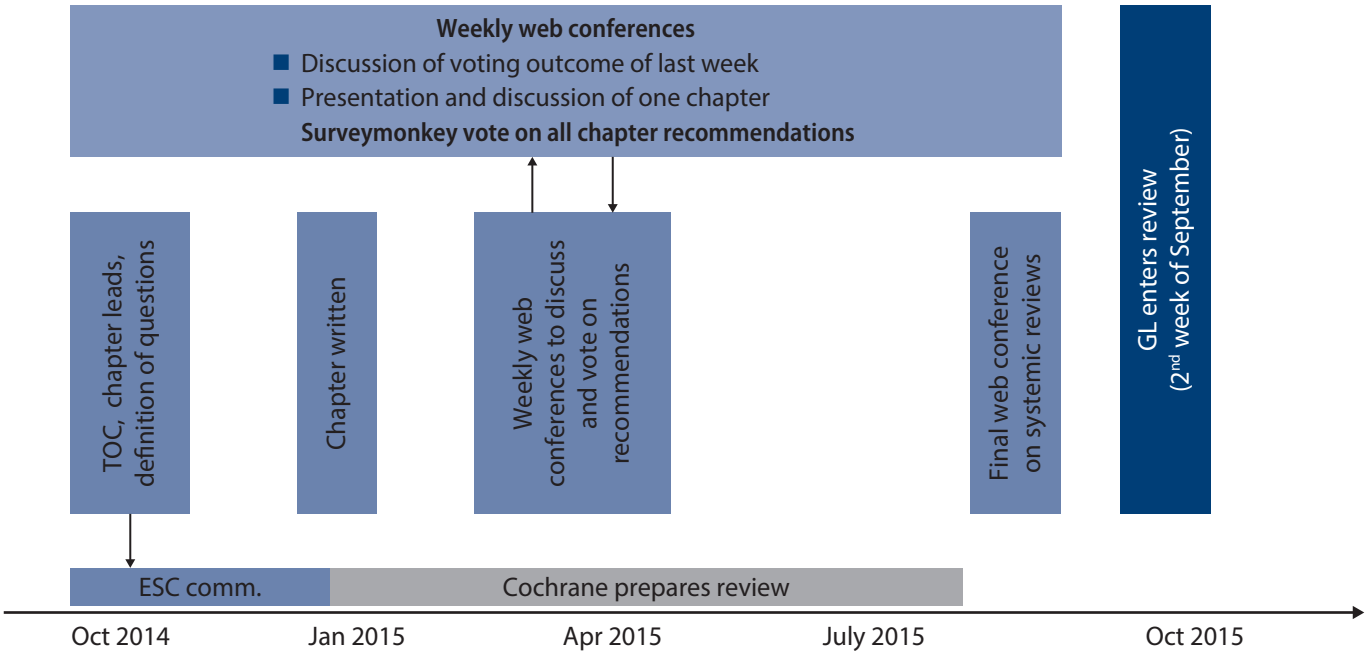
Source: Kirchhof P, Curtis AB, Skanes AC et al. Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology/ European Heart Rhythm Association/ European Association of Cardiothoracic Surgeons, the American College of Cardiology Foundation/ American Heart Association/ Heart Rhythm Society, and the Canadian Cardiovascular Society. Eur Heart J 2013; 34: 1471–7.

Figure 3: Comparison of European (ESC), US (ACCF/AHA/HRS), and Canadian (CCS) guidelines on atrial fibrillation. Blue (antiarrhythmic drugs) and green boxes (catheter ablation) mean agreement between the US and European guidelines while red boxes indicate differences (4).

Practical aspects of ESC guideline development using the example of the guideline on atrial fibrillation

In 2014/15, a new guideline on atrial fibrillation was developed in a collaboration between the ESC and the European Association for Cardio-Thoracic Surgery, EACTS5. At that time, the ESC agreed to commission systematic reviews in a pilot project together with the Cochrane Collaboration about several specific questions, e.g. „Efficacy and

Description of the process: guideline development within one year



Source: own presentation

Figure 4: Overview of activities and timelines in the development of the guideline. First, the structure was defined, followed by the chapter leads and the questions for the Cochrane Reviews.

safety of ablation in patients with non-paroxysmal AF" or „Concomitant surgical therapy for AF in patients undergoing cardiac surgery".

These questions were defined by the ESC Guideline Task Force. The definition criteria for the questions were primarily topics with a high degree of clinical uncertainty, e.g. where several smaller studies were available, but the evidence base was not sufficient and secure and new, or class 2 recommendations were advised.

From the order until the availability of the reviews, the Cochrane Collaboration took approximately six months. Independently of the guidelines, the respective reviews were published in the Cochrane Database of Systematic Reviews.

The integration of this further step into the workflow of the Task Force in the given period of about one year presented significant challenges. Figure 4 provides an overview of the main activities and timelines in the development of this guideline. First, the structure was defined, the chapter leads identified, and the questions for the Cochrane Reviews defined. During weekly virtual conferences, the individual chapters were then presented, discussed, and

voted on the recommendations. The votes were taken using the IT-based Surveymonkey methodology (https://www.surveymonkey.com). The results of the systematic Cochrane reviews were incorporated in a final virtual conference. Then, the review process started. In terms of time, these challenges could only be met within a year because the Cochrane Group started the review work very promptly, in some cases as early as October 2014 (see figure 4).

Meanwhile, each ESC task force has an expert in meta-analyses. This simplifies the processes, as the required meta-analyses can be prepared internally.

ESC-Guidelines: A Case for Collaboration

A good, intensive collaboration across different stakeholder groups and disciplinary and national boundaries with a high level of commitment, is an essential prerequisite for successful ESC guideline work:

The evidence on which the guidelines are based should be generated from large, ideally worldwide, studies;

- The thorough review of this evidence is time and resource intensive. Collaboration, e.g., with the Cochrane Collaboration, or in-house expertise in summary analysis of published data can provide essential support;
- English as the lingua franca of the life sciences is the starting point – with subsequent national adaptations and translations in the context of the national care situation;
- In an international context, similarities outweigh differences in recommendations;
- The diversity of national care situations provides the opportunity to learn from each other in terms of best practice examples.

Consequently, a close European cooperation is of high and trend-setting relevance for cardiology guidelines, especially against the background of the increasing Europeanisation of benefit assessment.

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Fast development of good guidelines – learnings from the AWMF-COVID task force

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The development of the COVID 19 guidelines is characterised by an enormous dynamic. Up to now, two S3 guidelines, one S2k guideline and fourteen S1 recommendations for action have been developed within a period of less than two years. Based on the corresponding mandate from the BMG in April 2020, the key success factor was the enormous commitment of a small, very agile, and well-networked working group. With the support of CEOSys as an evidence group and the COVRIIN expert group of the Robert Koch Institute, a very efficient infrastructure was established in a short time enabling timely elaboration of high-quality recommendations and guidelines. Some treatment recommendations, e.g. on the use of steroids or disease-stage-adapted anticoagulation, only came up during the development leading to the currently valid S3 guideline. Moreover, the high workload of the working groups involved must be viewed critically. For almost two years, they worked almost 24/7 on a voluntary basis. A core demand resulting from the experience with the COVID-19 guidelines is thus the continuation of the funding of the AWMF and the specialist societies involved.

Overview of the development of the COVID guidelines

The development of the COVID-19 guidelines is characterised by an enormous dynamic. In March 2020, a recommendation for the intensive medical treatment of COVID-19 patients was published for the first time.[2] Due to the poor data at that time, these first recommendations were mainly based on observations from China and Italy.

In April 2020, the German Federal Minister of Health asked the AWMF to elaborate COVID-19 guidelines. For this purpose, a task force was set up with 44 professional societies and the AWMF that is involved in the development of guidelines and their updating, sometimes on a monthly basis. A wide range of guidelines and recommendations for action were developed in a very short time. Up to now (December 2021), the AWMF website contains two S3 guidelines (inpatient therapy and prevention and control of SARS-CoV-2 transmission in schools), one S2k guideline (rehabilitation), and 14 S1 recommendations for action (figure 1a). Furthermore, eight guideline projects were registered (figure 1b).

From the beginning, work was characterised by enormous time pressure and emotional pressure. On the one hand, there was an urgent need for effective treatment procedures and corresponding recommendations; on the other hand, the evidence base for certain therapeutic approaches was extremely limited at the beginning, which significantly impaired clear recommendations for or against, e. g. the administration of vitamins or ivermectin, a pharmaceutical that has primarily been approved for use against parasites. Figure 2 provides an overview of the history of the COVID guideline on inpatient and intensive care therapy for this condition. Three steps can be derived from these recommendations:

Step 1: S1 guidelines (June 2020)

In June 2020, S1 guidelines for the intensive medical care of COVID-19 patients were published for the first time.[3] This was an update of the recommendation for intensive medical therapy of patients with COVID-19 published a few months earlier.[2] It mainly presented available data and corresponding – restrained or negative – recommendations on pharmacotherapy with chloroquine and hydroxychloroquine, antiviral substances (lopinavir/ritonavir), and on the use of immunomodulatory therapies with steroids based on the RECOVERY study from Great Britain or with tocilizumab, respectively. The use of chloroquine/hydroxychloroquine, lopinavir/ritonavir, or tocilizumab was not recommended outside of clinical trials. The guideline also includes an initial – optional – recommendation including a „flow scheme" for device-based therapy escalation in acute respiratory failure.

Step 2: S2k guidelines (November 2020)

The main innovation in the update of S2k guidelines in November 2020 was the recommendation on standard thromboembolism pharmacoprophylaxis. Moreover, treatment with remdesivir, preferably in the early phase of the disease, was included in the guideline as an „optional" recommendation.[4,5]

Step 3: S3 guidelines

In February 2021, guideline level S3 has been reached. The currently available version of the guideline reflects the status of 5 October 2021.[6] The guideline group could draw on a series of Cochrane Reviews based on the CEOsys project (Covid-19 evidence ecosystem). CEOsys is a project funded by the University Medicine Network of the German government that collects, evaluates, and summarises the results of scientific studies on major questions regarding the prevention, treatment and consequences of COVID-19.

Important innovations and additions include target values for adequate oxygenation in acute hypoxaemic respiratory insufficiency and the recommendation for prone positioning in patients receiving high-flow oxygen therapy. In addition, the recommendations for device-based therapy escalation in acute respiratory insufficiency due to COVID-19 and the recommendations for anticoagulation for different patient groups were differentiated. The optional recommendation in the S2k guideline for therapy with remdesivir was differentiated and partly weakened depending on the severity of the disease. In hospitalised patients requiring oxygen support and invasively ventilated patients,

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COVID-19 guidelines and recommendations for action

Lead professional societies:	Guideline title:	Status/Classification:
Prevention/protective measures:		
DGHM/GfV	↑ Prevention of infection by wearing masks	04 November 2020/S1
DGKJ, DGEpi, DGPI	↑ Measures to prevent and control SARS-CoV-2 transmission in schools – Living guideline	26 November 2021/S3
DGHNO-KHC, DGCH	↑ Interdisciplinary coordinated recommendations for staff and patient protection in the protection of staff and patients during scheduled procedures at the time of the SARS-CoV-2 pandemic	12 June 2020/S1
DIVI	↑ SARS-CoV-2 infection in healthcare workers - recommendations for testing by RT-PCR	11 September 2020/S1
DGAI	↑ Recommendations for training of health care workers during the COVID-19 pandemic	01 November 2020/S1
DGZMK	↑ Handling of dental patients exposed to aerosol-transmissible pathogens	08 March 2021/S1
Outpatient care		
DEGAM	↑ SARS-CoV-2/COVID-19 Information and practical aids for GPs in private practice	24 November 2021/S1
DGPflegewissenschaft	↑ Home care, social participation and quality of life in people with care needs in the context of outpatient care under the conditions of the COVID-19 pandemic – Living guideline	22 December 2020/S1
Inpatient care		
DGIIN, DIVI, DGP, DGI	↑ Recommendations for inpatient therapy of patients with COVID-19	13 October 2021/S3
DIVI, AEM	↑ Deciding on the allocation of resources in emergency and intensive care medicine in the context of the COVID-19 pandemic – Clinical ethical recommendations	30 April 2020/S1 (confirmed 16 July 2020)
Treatment of special patient groups		
DGPneumologie	↑ Post-Covid/Long-Covid	12 July 2021/S1
DGHO	↑ Coronavirus infection (COVID-19) in patients with blood and cancer diseases	03 May 2021/S1
DGN	↑ Neurological manifestations in Covid-19 patients	22 February 2021/S1
DGNR	↑ SARS-CoV-2, COVID-19 and (early) rehabilitation	01 November 2021/S2k
DGRheumatologie	↑ Care of patients with inflammatory rheumatic diseases in the context of the SARS-CoV2/COVID-19 pandemic	06 July 2021/S1
DGPflegewissenschaft	↑ Social participation and quality of life in inpatient care for the elderly under the conditions of the COVID-19 pandemic	17 August 2020/S1
DGVS	↑ Addendum to the S3 Guidelines on Crohn's Disease and Ulcerative Colitis "Care of Patients with Chronic Inflammatory Bowel Disease in the COVID 19 Pandemic"	26 April 2021
DGPalliativmedizin	↑ Recommendations for the treatment of patients with COVID-19 from palliative medical practice	29 June 2021/S1

Source: https://www.awmf.org/die-awmf/awmf-aktuell/aktuelle-leitlinien-und-informationen-zu-covid-19/covid-19-leitlinien.html

Figure 1a: Currently, two S3-level guidelines, one S2k guideline, and 14-S1 treatment recommendations on COVID-19 are available on the AWMF homepage.

COVID-19 guideline applications

Lead professional societies:	Guideline:	Classification:
DGN	† Neurological manifestations in Covid-19 patients	S2k
DEGAM	† SARS-CoV-2/COVID-19 Information and practical aids for general practitioners – Living Guideline	S2e
DGGG	† SARS-CoV-2 in pregnancy, birth and postpartum period	S2k
Treatment of special patient groups		
DGPflegewissenschaft	† Home care, social participation and quality of life in people with care needs in the context of outpatient care under the conditions of the COVID-19 pandemic – Living guideline	S2k
DGHO	† Coronavirus infection (COVID-19) in patients with blood and cancer diseases	S1
DGVS	† Treatment of liver transplant patients during the COVID-19 pandemic	S1
DGKJ, DGEpi, DGPI	† Measures to prevent and control SARS-CoV-2 transmission in schools - Living guideline	S3
DIVI, AEM	† Deciding on the allocation of resources in emergency and intensive care medicine in the context of the COVID-19 pandemic – Clinical ethical recommendations	S1

Source: https://www.awmf.org/die-awmf/awmf-aktuell/aktuelle-leitlinien-und-informationen-zu-covid-19/covid-19-leitlinien.html

Figure 1b: Overview of notified COVID-19 guidelines (as of December 2021)

remdesivir therapy was discouraged with a strong recommendation. Dexamethasone is the only pharmaceutical with a target recommendation. The other substance groups (JAK inhibitors, tocilizumab or specific antibodies such as casirivimab + imdevimab) have weak recommendations for individual degrees of disease severity.

The COVRIIN expert consultation – one example of a „living document"

The Specialist Advisory Group on Intensive Care, Infectious Diseases and Emergency Medicine (COVRIIN) consists of leading representatives of the German Interdisciplinary Association for Intensive Care and Emergency Medicine, the German Society for Infectious Diseases and the Standing Working Group of Competence and Treatment Centres for Diseases Caused by Highly Pathogenic Agents (STAKOB). The COVRIIN expert group aims at providing highly specialised expert knowledge from the respective specialist fields and evaluate and comment on complex interrelationships in the treatment of COVID-19 patients in an interdisciplinary manner. The three main topics of the specialist groups are i) the preparation of practical advice on the treatment of COVID-19; ii) advice on strategic patient transfer in Germany, and iii) telemedical support for intensive care units in Germany and internationally (see figure 3).

The corresponding COVRIIN homepage is operated by the Robert Koch Institute.[7] Especially the above-mentioned first main topic contains a lot of practice-oriented and up to date references to the treatment of COVID-19 (therapy overviews; therapy algorithms; infographics; recommendations for pharmacological and non-pharmacological treatment, etc.), practice reports, statements, and therapy recommendations. Figure 4 shows the presentation of dexamethasone from table 1 of the recommendations for

Overview of the development of the COVID-19 guideline

12 March 2020	**Recommendations** for **intensive care** therapy of patients with COVID-19
16 June 2020	**S1 guideline** – Recommendations for intensive care therapy of patients with COVID-19
21 July 2020	Update of S1 guideline – Recommendations for intensive care therapy of patients with COVID-19.
23 November 2020	**S2k guideline** – Recommendations for **inpatient** therapy of patients with COVID-19
23 February 2021	**S3 guideline** – Recommendations for inpatient therapy of patients with COVID-19
17 May 2021	Update of S3 guideline – Recommendations for inpatient therapy of patients with COVID-19
05 October 2021	Renewed update of S3 guideline – Recommendations for inpatient therapy of patients with COVID-19

Source: Professor Karagiannidis

Figure 2: Overview of the history of the COVID guideline on inpatient and intensive care therapy for this condition.

pharmacotherapy in COVID-19 with the evaluations of the COVRIIN expert group of the Robert Koch Institute.[8]

Tables include all other currently discussed treatment options. Current overviews and treatment recommendations of the COVRIIN group are also made available to a wider audience through regular publications in the „Deutsches Ärzteblatt" (cf. [9]). These recommendations for action are updated weekly in accordance with the guideline but are subject of a different formal process. Weekly updated documents can go hand in hand with a guideline and once again complement and strengthen it (figure 4).

„Living guidelines" – Preliminary conclusion using the example of the COVID-19 guideline

In the context of the COVID 19 pandemic, a high number of up to date, interdisciplinary and high-quality guidelines and treatment recommendations were produced in a short period of time under a high time pressure and high stress for all stakeholders. The key to this success was – among other things – the direct involvement and great support provided by the AWMF. Thanks to the mandate from the BMG in April 2020, the enormous commitment of the small and very agile, well-networked working group and the establishment of CEOSys as an evidence group supported by the University Medicine Network, a very efficient infrastructure was established in a short time which enabled a timely development of high-quality recommendations and guidelines.

Some therapy recommendations only came up during the development towards the currently valid S3 guideline:

- E. g. at the beginning of the pandemic, steroid therapy was rather not recommended – in contrast to the clearly positive recommendation for dexamethasone treatment in the current guidelines (see figure 4).
- The recommendations on anticoagulation have become more and more specified in the course of the development of the guidelines. The rather aggressive anticoagulation even in the late stages of the disease is no longer recommended in the current version.
- The significance of antiviral therapy with remdesivir remains controversial.

Overall, the high workload of the working groups must

Interdisciplinary expert group COVRIIN at the Robert Koch Institute

Specialist group – COVRIIN

Expert advice on COVID-19 at the interface, intensive care, infectiology, and emergency medicine

The Division of Intensive Care Medicine, Infectious Diseases and Emergency Medicine (abbr: COVRIIN Division) supports and advises the Robert Koch Institute on overarching specialist issues in the management of COVID-19 cases.

The aim of the specialist group is to provide highly specialised expert knowledge from the fields of intensive care medicine, infectious diseases and emergency medicine and to evaluate and comment on complex interrelationships in the care of COVID-19 patients in an interdisciplinary manner.

Main topics of the specialist group

1) Practical advice on the therapy of COVID-19

The COVRIIN specialist group compiles overviews of possible therapeutics for the treatment of COVID-19 with findings from practice for practice.

For more information, see Notes on therapy and care

2) Advice on strategic patient transfer in Germany

The COVRIIN specialist group advises the federal states and hospitals on questions regarding the strategic transfer of COVID-19 cases in Germany according to the so-called cloverleaf concept.

For more information, see Strategic patient transfers

3) Telemedical support

The COVRIIN specialist group advises and supports intensive care units in Germany and internationally in the treatment of complex COVID-19 cases through telemedical connection to Charité Universitätsmedizin Berlin.

For more information, see Telemedical support

Source: https://www.rki.de/DE/Content/Kommissionen/COVRIIN/FG_COVRIIN_node.html

Figure 3: The COVRIIN expert group aims at providing expert knowledge from the respective specialist fields and evaluate and comment on interrelationships in the care of COVID-19 patients in an interdisciplinary manner.

Excerpt from the therapy overview of the COVRIIN specialist group at the Robert Koch Institute

Substances (alphabetical)	**Approval status/ Availability**	**Data situation**	**Evaluation**
Anti-inflammatory therapy			
Dexamethason Dos.: 6 mg/d i.v. or p.o. once daily* Duration: max. 10 days[1] SE: typical known steroid SEs, infections (esp. fungal infections), moderate leukocytosis, lymphopenia, hyperglycaemia, gastrointestinal ulcers, gastrointestinal bleeding *Dosing during pregnancy between 23+5 and 34+0 WG: d1-d2: 2× 6 mg i.v. d3-d10 6 mg p.o./i.v. (see above) **No intramuscular administration due to** risk of bleeding under anticoagulation	**Approved as of O_2 requirement for ≥12 y and ≥40 kg**[2]	Randomised, placebo-controlled study: ✓ **RECOVERY**[3] o reduction in 28 day mortality o **Strongest benefit with invasive ventilation** o **Benefit with therapy initiation ≥ 7 days** after symptom onset o Less pronounced reduction in mortality with non-invasive ventilation therapy or low-flow oxygen therapy o **Possible negative effect in patients without O_2 administration** Randomised, blinded study: ✓ **COVID STEROID 2 Trial** [4] COVID-19 pat **with severe hypoxaemia** (O_2 10 l/min, NIV, IV* n=971) **Dexamethason 12 mg vs Dexamthason 6 mg**, median 2 days after hospitalisation o Primary endpoint days without *life support* (IV, catecholamines, extracorp. renal replacement procedures) on d28: 22 vs 20.5; with no significant difference o Secondary endpoint: Days without *life support* at d90 84 vs 80; no significant difference o **Secondary endpoint: Days survival and stat. discharge at d90: 61.5 vs 48 (CI 95% -1.3–9.5; p 0.09): no significant difference, but clear trend for dexamethasone 12 mg** *IV: Invasive ventilation	➢ Indicated **for any form of new-onset or worsening O_2 requirement (including low/high flow therapy, non-invasive and invasive ventilation)** ➢ **Earlier use** unlikely to confer benefit and **may even be detrimental** ➢ Co-administration of remdesivir is possible ➢ Administration of **tocilizumab only with dexamethasone comedication** (see here)[5,6] ➢ As **comedication to JAK inhibitors as soon as O_2 supplementation** is necessary (see there)[7,8] ➢ **In severe hypoxaemia (O_2 min. 10 l/min, NIV, IV) and lack of availability of tocilizumab or baricitinib,** early doubling **of the dosage (dexamethason 12 mg q24h)** can be beneficial **in individual cases**[4] ➢ Impact on viral clearance is unknown ➢ Careful observation regarding secondary infections ➢ **In pregnancy,** additional benefit of **antenatal steroid prophylaxis** ("lung maturity") between 23+5 and 34+0 WG.

Source: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Therapieuebersicht.pdf?__blob=publicationFile

Figure 4: Recommendations for pharmacotherapy in COVID-19 with evaluations of the COVRIIN expert group – using the example of dexamethasone.

be viewed critically. For almost two years, they worked almost 24/7 on a voluntary basis. The achievements of the working groups and the AWMF were only partially supported and also financially rewarded by politics. A core demand resulting from the experience with the COVID-19 guidelines is thus the continuation of the funding of the AWMG and the involved professional societies.

Editorial support: Professor Jörg Ruof

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Clinical guidelines – the European perspective

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The progress and structure of guideline programmes across Europe are highly variable. Collaboration and knowledge transfer can play a key role in this area. Research funding contributed to major achievements in the development or implementation of guidelines and the European Union has a number of instruments that can be used to support guideline programmes.

In 2001, Europe's leading human rights organisation, the Council of Europe, already recommended the member states to develop a coherent and comprehensive set of rules for the production and implementation of clinical guidelines in line with internationally accepted good practice.[1] At the same time, the importance of international networking among organisations, research institutions, clearing houses, and other entities that create evidence-based medical information was emphasised.

What does the implementation of these recommendations look like? The last comprehensive survey of practices in the development and application of clinical guidelines in European countries dates back more than ten years. Based on the Council of the European Union's conclusions on „Innovative Approaches to Chronic Diseases in Public Health and Health Systems" (December 2010), the European Commission supported the systematic mapping of current practice.

This was conducted by the European Observatory on Health Systems and Policies in 2011 with 80 respondents from 29 European countries.[2,3] Among other things, the survey examined the legal basis for guidelines in the respective healthcare systems, the process of guideline development, quality control mechanisms, implementation modalities, and the evaluation of the elaborated recommendations.

Ten years after the Council of Europe's recommendation, there is still no uniform picture. Overall, the study identified three broad categories of countries: Countries with „well-established" activities and extensive experience in both guideline development and implementation (including e.g. Belgium, England, France, Germany, and the Netherlands); countries that have adopted some form of guideline development and thus „approached" robust systems (e.g. Luxembourg); and countries where guideline de-

velopment structures were „in the planning phase“ or not yet planned at the time of the study.

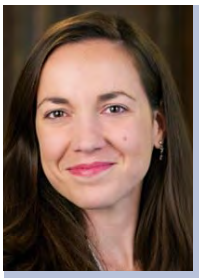
The structure of existing guideline programmes also varied: whereas in some countries a central institution or authority was responsible for guideline development in collaboration with health professional associations (e.g. France or Great Britain), in others development was centrally coordinated but conducted at different levels or by multiple stakeholders (e.g. Belgium or Norway). While implementation of guidelines was not mandatory in most countries, in well-established systems guideline-based treatment was expected (see figure 1). It is highly probable that the situation in many of these countries has evolved in the decade since the results were published (e.g. as in Greece and Slovenia).[3]

Nonetheless, a quick look into the Guidelines International Network (GIN, https://g-i-n.net/) guidelines library suggests that not even one third of all EU countries register their guidelines there (there is no similar repository at the EU level). Germany leads with 812 entries of guidelines at various stages of development, followed by the Netherlands with 319, Spain with 206, France with 170, Finland with 112, Denmark with 56, Belgium with 54, and Italy with 6. The United Kingdom, with the National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN), which are considered international role models, is represented with 302 entries as of January 2022.[4]

Could a stronger promotion of clinical guidelines at the European level promote their use? So far, the role of the EU in the development and implementation of clinical guidelines has not been particularly strong. Intuitively, this goes hand in hand with the limited competences of the EU regarding healthcare: While the Union is committed to ensuring a high level of health protection for its citizens, the competence of European healthcare systems to shape themselves autonomously must not be restricted in the process. Accordingly, EU health policy is intended to complement the Member States‘ policies and support their activities, as well as to promote their collaboration.[5]

There are several EU instruments for member states to use to strengthen their healthcare systems,[6] and in certain cases they have been used to support clinical guidelines. For example, the development of the most widely used guideline quality assessment tool (AGREE – Appraisal of Guidelines for Research and Evaluation) was initiated with funds from EU research funding.[7] A renewed focus on the importance of clinical guidelines for high quality healthcare in European countries has been reflected most recently with calls for topics for further research proposals under the current EU Horizon Europe funding programme.[8]

The main instrument for implementing the EU health strategy is the Health Programme (since 2021 EU4Health) funding e.g. various activities of the European Reference



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Implementation of clinical guidelines

- No obligation for most countries, and in the few countries where there is a mandate (e.g. Netherlands for end-of-life care) no clear pathways or penalties for checking compliance
- In well-established systems, there is already an expectation that guidelines will be followed (e.g. England: if deviating from NICE guidance, reasons must be clearly documented)
- Financial incentives rather rare ways of dissemination

Ways of dissemination

- Mainly websites of the responsible institution
- Additionally central repositories if there is a central mechanism
- Targeted initiatives, such as sending updated guidelines to all registered physicians, together with short version in simple language (e.g. Sweden), websites with interactive learning processes (e.g. Netherlands), integration in electronic patient records or practice management systems (e.g. Netherlands, Finland), smart phone apps (several, e.g. Spain)

Source: Legido-Quigley H, Panteli D, Brusamento S, Knai C, Saliba V, Turk E, Solé M, Augustin U, Car J, McKee M, Busse R (2012). Clinical guidelines in the European Union: mapping the regulatory basis, development, quality control, implementation, and evaluation across member states. Health Policy 107(2-3):146–56.
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Figure 1: The structure of guideline programmes varies widely across the EU member states. The ways in which guidelines are disseminated also vary, although common trends can be identified.

Networks introduced by the Directive on the application of patients' rights in cross-border healthcare (Directive 2011/24/EU). These virtual networks between healthcare providers and centres of expertise in EU member states have been collaborating in the management of rare or extraordinarily complex diseases. One of the activities comprises the development of clinical guidelines.[9,10]

EU-funded joint actions have also contributed to this, such as the Joint Action on Rare Cancers under the supervision of the German Cancer Society, the sixth work package has focused on identifying and evaluating relevant guidelines.[11] For some indications, the European Commission takes care of the development or update of guidelines, such as the European Commission Initiative on Breast Cancer (ECIBC), and provides support for the adoption and adaptation of recommendations in the member states on a voluntary basis.[12]

One essential common feature of these options is the collaborative approach to enable a knowledge transfer between the member states. It should be emphasised that transnational collaboration on clinical guidelines has been established quite well at several levels, e.g. in the framework of European professional societies who develop guidelines or in the networking of relevant stakeholders via the GIN (these aspects are addressed in more detail in other articles of this publication).

However, there seems to be room for improvement in the use of the EU instruments to promote clinical guidelines, despite the examples provided in this article. This applies both to the opportunities described and other mechanisms that could be used to establish or strengthen guideline programmes, such as the Technical Support Instrument (TSI).

The COVID-19 pandemic has brought the importance of resilient health system to the forefront. Well-established high-quality guideline programmes and systems of evidence generation or synthesis associated with them can play a key role here. Thus, it makes sense to invest in developing or strengthening them. In perspective, it should be determined how the EU's support capabilities could best be used to achieve this goal and improve knowledge transfer between countries without duplicating existing initiatives. And in doing so, relevant experience from HTA collaboration should also be taken into consideration.

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Up to date, digital and with greater utility: how guidelines can become even better

By Dr Florian Staeck

Germany has one of the most advanced registries of medical guidelines worldwide, including 192 S3 guidelines. This means that, at least theoretically, a wide range of findings from scientific medicine is available to physicians at the point of care. As defined by the Association of Scientific Medical Societies (AWMF), guidelines are systematically developed statements reflecting the current state of knowledge to support decision-making by physicians and health professionals, as well as patients, to ensure appropriate healthcare.

Thus, guidelines create a bridge between systematic review and the bedside – they provide up to date external knowledge as an aid for individual decision-making. The AWMF's logo reflects the networking character of the working group: Participants reported that the AWMF's Institute for Medical Knowledge Management, is responsible for maintaining the guideline registry with only seven full-time employees. However, it is supported by about 2,500 clinical experts in the respective field, who drive guideline development forward.

But the current decentralised structure of guideline development – based almost exclusively on voluntary initiatives in professional societies – is facing major challenges. On the one hand, the speed of medical-technical progress brings about a constant pressure to update guidelines. On the other hand, studies show that the use of guidelines by physicians still leaves much room for improvement – professional societies and guideline authors are responding to this with even greater efforts regarding readability and applicability. Some S3 guidelines are clearly obsolete.

But probably the greatest challenge lies in the digitisation of guideline knowledge – for use e.g. in physician information systems in clinics and practices, in information portals for patients and citizens, and in learning platforms for students. The participants at the 14th meeting of the Platform for Interdisciplinary Benefit Assessment, which took place as a hybrid format in Fulda on October 8-9, 2021, agreed on this description of the problem.

Against this background, participants unanimously welcomed the fact that in 2019 the legislator created the basis to financially support the development of quality-assured guidelines with the Digital Care Act (DVG). As a result of the amendment, the Innovation Committee of the Federal Joint Committee (G-BA) has been tendering for funding programmes since mid-2020. Participants reported that the first funding awards were granted in October 2020. Eleven programmes were dedicated to the development of guidelines for rare diseases, and eight others for guidelines for mental diseases.

A new regulation stipulates that the Institute for Quality and Efficiency in Health Care (IQWiG) can be commissioned with evidence research for the further development of guidelines. This was also acknowledged as an advancement since up to now, e.g. only 35% of all procedures for early benefit assessment have a current guideline in the relevant indication – the remaining procedures are reported to be the „white spots" of guidelines. High-quality guidelines were still lacking for diseases of significant importance to the population; migraine was mentioned as an example. Or in some cases, only guidelines were available with limited transferability to the German healthcare context.

The participants referred to the digitisation of guideline knowledge as the structurally greatest challenge – this incidentally included digital tools for guideline development. These could be an important motor to accelerate knowledge generation as required by medical-technical progress and the speed of publication in scientific journals. The participants pointed out that such a digital „evidence ecosystem" was, however, very pre-conditional, partici-

pants made clear. Uniform interoperability standards and open interfaces based on an existing methodology were required. Only this would enable a well-structured way of keeping guidelines based on a uniform data model.

The first pilot projects had already been conducted, but the actual implementation of such a digital infrastructure could not be financed from AWMF funds, participants noted. Corresponding research applications had not yet been approved by third-party funders. It was argued that a long-term national action plan for the digitisation of guideline knowledge was thus required for implementation.

One conclusion was that the legislator had recognised the importance of high-quality guidelines. However, the utilisation by the individual physician in the individual treatment situation presupposed that the knowledge condensed in guidelines has been prepared for this situation and can be retrieved. Participants explained that this knowledge would have to be transferred into medical terminology systems, such as SNOMED or ICD 10. Such data models were already available, at least in rudimentary form. Each individual recommendation from a guideline would have to be coded so that it is electronically available at the point of care when it is needed.

They said that the digitisation of guidelines was particularly urgent in view of the often insufficient use of guidelines in daily clinical practice. Different voices were raised in this regard during the meeting. On the one hand, studies were cited according to which guidelines were appreciated but underutilised by general practitioners (GPs). According to one study, only 28 percent of GPs used national healthcare guidelines. A study revealed that 71 percent of GPs preferred to rely on their own approach, although 80 percent of respondents understood that guidelines enable a structured approach to diagnosis and treatment.

This was countered by the fact that a distinction should be made between the explicit and implicit reception of guidelines. According to this, GP care was much more permeated by guidelines than the results of the survey indicated. E.g. guideline knowledge was included in continuing education and was available at one click in medical information systems in GP practices. However, the quality circle work should be expanded, in which GPs receive feedback on the extent to which their prescriptions comply with the guidelines through systematic individual prescription analyses, participants said.

Against this background, the participants of the 14th Platform Meeting discussed the following aspects:

- **Learning experiences from the development of „living guidelines" in the context of COVID-19:** As a particular case of guideline development, meeting participants discussed the guidelines that have been developed in the context of the Corona pandemic. The challenges here were having to make decisions in a short period of time and under great external pressure – and this despite the fact that knowledge about COVID-19 was initially very incomplete and growing rapidly. Based on the recommendations on intensive care therapy in March 2020, an S1 guideline was developed by June 2020. This was followed by an S2k guideline in November of the same year and finally an S3 guideline in February 2021. The key to this success was an initially small but highly active group of highly committed guideline authors. Other positive factors were the direct commissioning by the Federal Ministry of Health and involvement of the AWMF in the guideline development process.

It was always important for the AWMF guideline network to have a triad of guidelines at all stages of development. This was summarised in the metaphor that „reliable tankers" were required in the form of S3 guidelines, „tugs" that get these tankers on the move in form of S1 and S2

guidelines, and „speedboats" of availability and topicality, such as oncology guidelines on ONKOPEDIA.

The CEOsys project, funded by the German government through the University Medicine Network, was highlighted as an important structural feature that also enabled „lifting" the guideline to S3 level. This is an association of

20 German university hospitals and non-university partner organisations. Through CEOsys, „living" evidence syntheses have become possible, which are constantly kept up to date by including new study results. The critical handling of preprints, i.e. publications in journals that have not yet undergone a formal peer review process, has proved to be a particular challenge which was hardly known before. The extraordinarily high workload of the authors involved – in addition to a busy clinical routine – over a period of months in case of the COVID-19 guidelines was described as a classic example of „self-exploitation".

It highlights the lack of structural support for guideline groups starting with basic issues as the lack of secretariats to support the scientists involved, they said. Participants urged that the high level of attention due to COVID-19 should be used to bring this urgent concern to the attention of health and science policy makers, who will be engaged in coalition negotiations in October 2021.

As a first yet very important step towards achieving structural support of professional societies, the participants welcomed a contractual agreement between AWMF and the G-BA in autumn 2021, according to which all inquiries in the context of the early benefit assessment would be remunerated to the professional societies as commissioned work. The participants valued this as a constructive approach to support the work of professional societies.

- **Success criteria for the actual application of guidelines in the healthcare context:** Participants described it as challenging to find a balance between a guideline that was useful in the healthcare context and could be implemented, and at the same time meets the highest quality standards. Success factors for the penetration of guidelines into the daily clinical practice could certainly be identified, they said. For example, guidelines should be easy to apply – an implementation into physician information systems was a conceivable aid here. Furthermore, guideline recommendations required a clear legal basis. A further factor highlighted was the compatibility of guidelines with remuneration schemes, so that recommendations for action could be implemented in a cost-covering manner. This applied in particular to marker diagnostics and special imaging techniques.

Other participants emphasised the utility of algorithms to clearly present complex treatment and therapy regimens. They outlined that guidelines of several hundred pages were only read by very few physicians and condensed versions of 10 to 40 pages would be needed. In addition to topicality, (digital) accessibility and clarity were therefore important success factors.

The participants argued that the desire for continuous updating of guidelines was also associated with the risk of a mismatch between relevance to healthcare, the additional knowledge gained, and the resources required for updating. It was a matter of common sense to manage financial and human resources carefully. Some participants warned of a hasty guideline updating and pleaded to wait for the analyses of HTA institutions such as IQWiG after the approval of a new pharmaceutical.

The attempt to merely supplement guidelines with amendments quickly reached its limits. They also argued that a new pharmaceutical could change the entire „statics" of a guideline. Consequently, the entire diagnostics and therapy would then have to be re-examined and re-

evaluated – with the corresponding consequences for the duration of the revision.

The complexity of guidelines for individual disciplines was described as a further challenge which hardly allowed the reception by non-specialists, e.g. by GPs. In view of this, sceptical comments were made on whether individual segments of complex guidelines could be separated. This was countered by the argument that splitting guidelines into different sub-documents would make their timely updating very difficult or even impossible. The better alternative in this situation could be a joint guideline from several professional societies.

- **Pros and cons of the use of European guidelines:** The participants controversially debated potentials and problems in the preparation of European guidelines. The supporters argued that European collaboration could also be helpful for Germany since the generation of evidence was costly, time and resource intensive, this process could be centralised if the right partners were available. As a result, it made sense to write guidelines in English, as the lingua franca of scientific medicine, they said.

While there were differences in the treatment structure in individual countries, in the end the similarities were greater than the differences. Other participants objected that important professional societies at European level worked predominantly on an industry-sponsored basis. Many corresponding guideline authors also had relevant relationships with industry. Thus, it was better to rely on national consensus.

The thesis that the partly major differences in the national healthcare systems could nevertheless be represented in a European guideline was also contradicted. This was countered by the argument that best practice could be learned from the heterogeneity of healthcare, especially regarding a large number of countries. This would not be possible with national guidelines.

- **Impact of the future EU-wide Health Technology Assessment on guidelines:** The participants debated with different tenor about the consequences of benefit assessments for new pharmaceuticals and medical devices at European level, the so-called EU HTA Regulation. After long negotiations, an agreement on future joint benefit assessments took shape in summer 2021, which shall start gradually from 2025. The focus will initially be on oncology products and orphan drugs.

On the one hand, participants said that the guideline community saw it as helpful if HTA organisations agreed on a common methodology. This would enable better pooling of existing resources. On the other hand, participants warned against overestimating the importance of the EU HTA process for the AMNOG process. At present, an „HTA light process" was emerging in the EU, which would neither substantially affect healthcare nor the national pricing procedure in Germany. Therefore, the argument goes, the EU HTA Regulation would probably provide little sustainable impetus for the development of guidelines.

- **Perspective of research-based pharmaceutical companies on guidelines:** The participants reported, that in research-based pharmaceutical companies the design of phase 3 studies was usually based on national or international guidelines. The question for the companies here was to what extent the guidelines reflected healthcare and thus the costs for the statutory health insurance, they said. The reason for this was that it was very difficult to address specific care conditions in individual countries in clinical studies. With regard to the early benefit assessment, the differences between international guidelines and the specifications of the G-BA – for example with regard to the appropriate comparative therapy (ACT) – were described as problematic.

Therefore, the participants also objected to the inclusion of benefit assessment decisions of the G-BA in a guideline. They argued that AMNOG was not designed for healthcare management, but rather as an instrument for fair price negotiations. Evidence-based clinical treatment recommendations would thus have to remain separate from the formal processes of price determination.

Again, they emphasised that guidelines would have to be a reliable source of information for daily clinical practice according to the standards of evidence-based medicine. And this, of course, also included the use and critical appraisal of existing public sources of information – thus also the corresponding IQWiG and G-BA documents. Against this background, it should be viewed critically if a guideline does not include a substantive discussion of the decisions of the G-BA – especially if most pharmaceutical in one indication had undergone the AMNOG procedure, they said. Although G-BA-decisions on additional benefits were aimed at fair pricing, they were always also relevant to the provision of healthcare when it comes to compliance with the requirement for cost-effectiveness in accordance with Section 12 of the SGB V.

The participants outlined that there were several examples of the plausibility of such an approach, e.g. a new active ingredient could fail due to the methodological requirements of the AMNOG procedure and still be the treatment of choice for treating physicians. The contextualization of a G-BA decision could also be urgent if different assessments of equivalent treatments had occurred over time, e.g. because the ACT had changed in the meantime. Finally, combination therapies might have been evaluated differently by the G-BA, and here, too, the classification of these decisions in a guideline would be reasonable.

- **European dimension:** The participants concluded that a look at other European countries showed that the development of guidelines had only been systematically promoted in a few cases in the past. Financial incentives for the development of guidelines are as rare to find as fixed intervals for updating them. Bilateral initiatives – e.g. in the sense of a Franco-German axis – were considered to be only conditionally promising. This was because in France, the government or the Ministry of Health were key players in the development of guidelines, while in Germany, the AWMF mainly had moderation and quality assurance tasks. In view of these completely different dialogue levels, it would be difficult to expect any impetus from a stronger Franco-German cooperation.

As a conclusion, the participants of the 14th meeting of the Interdisciplinary Platform stated that in Germany the network moderated by the AWMF forms the „backbone“ of the development and updating of guidelines – and not a single institution such as NICE in Great Britain. Therefore, the focus should remain on strengthening the structural requirements of this network – also in financial terms.

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Guidelines – their role in AMNOG and medical care

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