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Interaction between HTA and authorisation

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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 and Association of Research-Based Pharmaceutical Companies (vfa e.V.).

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

Convergence or divergence of HTA and authorisation: which benefits patients and society more?

Professor Jörg Ruof

Dear readers

One of my favourite quotes from the EU HTA regulation can be found in paragraph 3. It states: „HTA is able to contribute to the promotion of innovation, which offers the best outcomes for patients and society as a whole and is an important tool for ensuring proper application and use of health technologies."

This objective can certainly be agreed upon by all stakeholders and also applies to a large extent to the assessment of risk and benefit by the regulatory authorities. In his opening presentation, Mr Broich described the role of the BfArM as an „enabler and driver of ideal healthcare provision."

However, as always, the difficulties arise when trying to implement this objective in practice. It is widely known that:

- on the one hand, innovative pharmaceuticals are almost always approved more quickly in the USA and are available to patients earlier in the healthcare system, and
- on the other hand, data on the safety and efficacy profile compared to the current standard of care is only available for some of the new pharmaceuticals at the time of authorisation, yet this data is essential for the HTA process.

This publication addresses the tension between the authorisation and HTA processes. The strategic fundamental questions are outlined at the beginning of the publication:

- Ms Haas raises the question of whether the two-stage process of authorisation and HTA assessment makes sense or whether there should be greater convergence of the two processes in the future.
- In his theses on the strategic further development of authorisation and benefit assessment, Mr Hebborn emphasises the independence of regulatory and HTA procedures and the necessary differentiation of these two processes.

The aim of the Platform on Benefit Assessment and this publication is not to resolve this contrast, but rather to analyse the associated arguments and considerations as thoroughly as possible. The methodological article of Mr Bucher, for example, addresses the different ways of dealing with uncertainty in the authorisation and HTA processes using the example of Joint Scientific Advice. Mr von Kalle and the working group of the Berlin Institute of Health open up horizons beyond the established comparative instruments of randomised controlled therapy studies and address the perspective and integrative collection and use of data and the generation and evaluation of real-world evidence, including the use of artificial intelligence.

The comments on the planned Registry Act by Mr Algermissen and the BMG working group present – appropriately – the corresponding framework for the future development and use of real-world evidence. The objectives, such as ensuring and further developing registries, establishing a standardised legal framework, and promoting the use of registries, support greater consideration in both authorisation and HTA procedures.

A critical view of the AMNOG, framed by the associated questions by Mr Wasem, is provided in Mr Gemmel's and Mr Lüdtke's article. It focuses on the specifics of the AMNOG assessment procedures for chronic diseases and calls for, among other things, the recognition of the primary endpoints of authorisation studies in HTA procedures, the reliability of advisory discussions, and the withdrawal of the guardrail regulation from the Financial Stabilisation Act (GKV-FinStG).

As at previous events of the Platform on Benefit Assessment, the perspective was extended beyond national

borders. In many European countries, such as Italy, Spain, and Austria, important sensitive reimbursement decisions for cost-intensive therapies are made at the regional level. The impact of the EU HTA Regulation on these decision-making structures remains to be seen. In her article, Ms Wild from the Austrian Institute for Health Technology Assessment illustrates how the EU HTA Regulation accelerates the legal anchoring of a national evaluation board in Austria.

Throughout the platform meeting, questions about the influence of the EU HTA Regulation on the interaction between authorisation and HTA procedures were repeatedly raised. Some of the procedural challenges associated with the EU HTA Regulation are exemplified in the interjection by Mr Jantschak from the KBV. It should be noted that the Implementing Act required under Article 15 of the EU HTA Regulation, which is intended to provide further details on cooperation and information exchange with the European Medicines Agency, was not presented until after the conference. Accordingly, it was not possible to refer to it in this publication, and it remains to be seen how the accents of this Implementing Act, which focuses on the exchange of information will affect the tension between convergence and divergence.

Many thanks to the speakers and authors of the publication – and to you, dear readers, I wish an engaging read of the articles.

Jörg Ruof

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Interaction between HTA and authorisation: Questions from the perspective of the National Association of Statutory Health Insurance Funds

Dr Antje Haas | Head of the Medicines and Remedies Department of the National Association of Statutory Health Insurance Funds

Separation or merging of authorisation and HTA

The authorisation process evaluates whether the benefit of a therapy outweighs its harm, typically compared to the absolute zero value „placebo". HTA seeks to determine whether, and to what extent, the benefit exceeds that of an established therapy.

Does this two-stage approach make sense, or should the authorisation process already include information (or depend on it) indicating that a new therapy actually improves care?

Evidence requirement for authorisation

In various therapeutic areas, such as multiple myeloma and other oncological diseases, there has been considerable progress with the development of many new pharmaceuticals.

Due to legal requirements for conditional marketing authorisation (CMA), many of these active substances are approved based on non-comparative, i.e. single-arm studies. The resulting challenges for comparative benefit assessment are well known.

Should there be a defined point in time at which a „medical care gap", required for a CMA, no longer exists, necessitating an RCT for authorisation – actively controlled due to the fatal progression of the disease if untreated?

When does a therapeutic area evolve to the point where e.g. single-arm studies, once acceptable for authorisation, are no longer sufficient?

Therapy pathways/therapy algorithms

In the oncological field, where potential curative treatments are involved, therapy concepts have been evolving over the years, including adjuvant, neoadjuvant, and perioperative therapies. This evolution presents significant challenges in the intention-to-treat (ITT) population:

- In adjuvant therapy, pharmacotherapy can be tested in isolation by including only patients in whom tumour resection was successful.
- Neoadjuvant therapy is more complex, as the resectability of the tumour is influenced by pharmacotherapy.
- Resection is an integral part of perioperative therapy.

How can authorisation and benefit assessment reflect that sometimes more aspects related to the therapist than the pharmaceutical are examined? And shouldn't there be a comparison of therapy concepts, at least during transitional periods? Ultimately, the cause of therapy success or failure is secondary to the patient.

Comparable therapeutic approaches

In many therapeutic areas, there is a coexistence of therapies targeting the same molecular target or therapies addressing new targets but showing similar benefits.

Should „first-in-class" versus „me-too" be a decision criterion in these cases? Should this be assessed during authorisation or only in the context of the HTA process? How could such an assessment be presented?

Dynamically changing therapy standards

The primary goal of authorisation is to demonstrate a positive risk-benefit ratio, not necessarily an improvement over the standard of care. HTA primarily questions the superiority to the current standard of care.

Fortunately, various indication areas show rapid development dynamic, which repeatedly poses a challenge, particularly in dynamic application areas. The standard of care, against which an additional benefit is to be demonstrated, changes faster than the studies can keep up.

- This raises the question of the required data basis for an

informative assessment for authorisation. How quickly should one react to changing therapy standards? How long are placebo-controlled studies informative in the authorisation process? Does this solely depend on whether they were ethically justifiable initially?

- Similar challenges arise for benefit assessment: What is the better approach to assess the additional benefit – an (indirect) comparison with the current standard of care (which may be methodologically difficult) or a direct comparison with an outdated therapy?

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Current topics and challenges – Benefit/risk assessment and HTA interaction

Professor Karl Broich, Dr Wiebke Löbker | Federal Institute for Drugs and Medical Devices (BfArM)

The Federal Ministry of Health's pharmaceutical strategy aims to prepare Germany for the future and enhance its appeal as a centre of research and development. The strategy focuses on simplifying and accelerating approval processes for clinical studies, reducing bureaucracy, increasing synergies between regulatory authorities, and promoting research and innovation projects. Concurrently, the Digital Act and the Health Data Use Act support digitalisation and data utilisation to improve healthcare and nursing care in Germany. At European level, these national initiatives are flanked by the establishment of a European Health Data Space and a future EU-wide benefit assessment of new therapies alongside European authorisation, strengthening Europe as a pharmaceutical location. In its role as an enabler and driver of ideal healthcare provision, the Federal Institute for Drugs and Medical Devices (BfArM) plays a crucial role in advancing these initiatives and objectives, both nationally and as a strong partner in the European regulatory network, in close collaboration with authorisation of pharmaceuticals and HTA assessment institutions.

The field of pharmaceutical development and medical technology is experiencing rapid progress driven by scientific and technological advancements, particularly increasing digitalisation. These advances lead to faster development cycles of pharmaceuticals and enable the introduction of innovative treatment methods within an expanding digital healthcare ecosystem. Germany plays a prominent role in pharmaceutical research and development, as evidenced by the swift development of the first COVID-19 vaccine and test during the COVID pandemic. Germany, alongside Spain, conducts most multicentre clinical studies in Europe[1], which underlines its prominent position as a major location for the development and manufacture of pharmaceuticals (figure 1).

Faster drug development cycles require close collaboration between research institutes, companies, and authorities. Germany provides an ideal environment for this collaboration due to its well-established infrastructure facilitating a swift translation of research findings into marketable products. Germany has also caught up significantly with other countries in the area of digitalisation in the healthcare sector in recent years, among other things thanks to the Digital Healthcare Act.

However, recent analyses indicate that Brexit, the pandemic, and other current crises have intensified competition in the healthcare sector, making Germany less attractive as a research and development location.[2] The pandemic has exposed vulnerabilities in supply chains, particularly due to reliance on a few manufacturing sites in third countries. Regulatory „lessons learned" from the pandemic highlight areas where authorisation and assessment procedures can be simplified. Challenges in organising clinical studies, accessing health data, and collaborating with academic research have been identified as national challenges for Ger-

many's innovation landscape.[2]

To position Germany for future comprehensive, modern healthcare and to enhance its attractiveness as a pharmaceutical location, several modernisation and reform projects have been launched at both national and European levels. These projects are integral components of the federal government's pharmaceutical and digitalisation strategy.[3,4] The BfArM, along with the Paul Ehrlich Institute (PEI), plays a vital role in the implementation and realisation of key projects.

Strengthening Germany as a centre of research and development for pioneering healthcare: from the pharmaceutical strategy to the Medical Research Act, Digital Act and Health Data Utilisation Act

Germany's pharmaceutical strategy aims to strengthen the country as a centre of science and research, promote innovation, and ensure patients have comprehensive access to safe and effective pharmaceuticals and innovative treatments. The strategy includes measures to promote and facilitate research and development, support start-ups and (small) companies, improve cooperation between industry, research, and government, promote healthcare system digitalisation, and modernise and reduce bureaucracy in regulatory processes.

The draft Medical Research Act (MFG)[5] is a central part of this strategy, aiming to strengthen medical research in Germany by improving the legal framework for clinical studies, simplifying bureaucratic processes and approval procedures, and facilitating access to research data. The following overview provides an overview of the central measures of the MFG (figure 2).

The establishment of an interdisciplinary ethics committee for complex studies at the Federal Institute for Drugs and Medical Devices (BfArM) is intended to simplify the planning and implementation of clinical studies. In additi-

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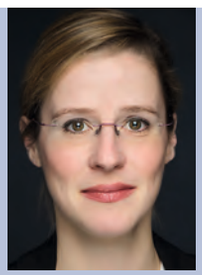
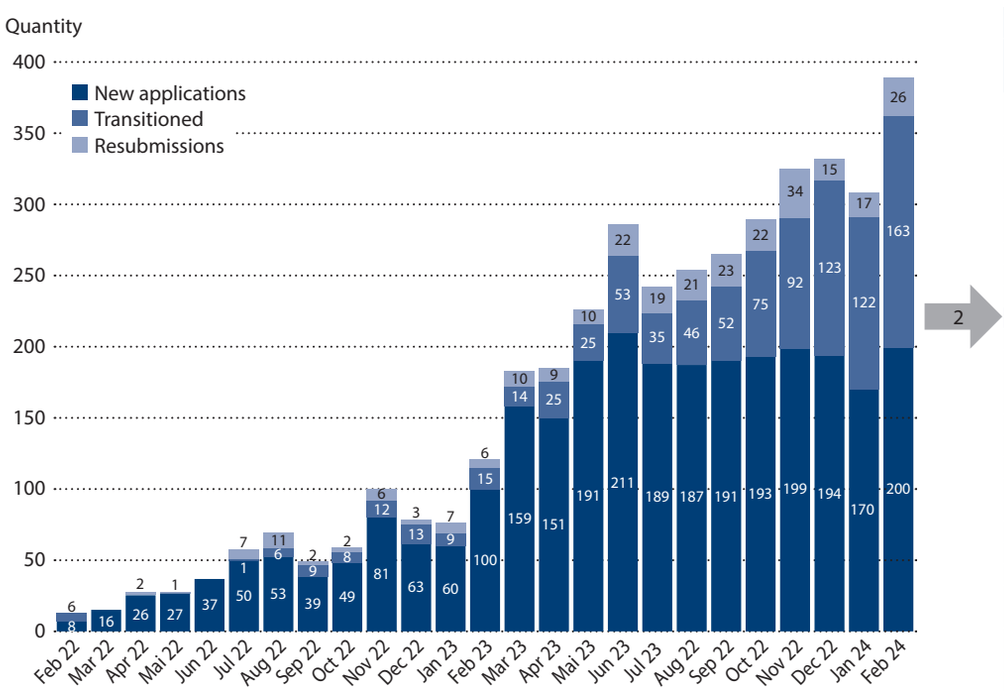


Dr Wiebke Antonia Löbker, *pharmacist (specialised pharmacist for drug information); 2009 to 2011 scientific associate at the Institute of Pharmacology of the Free University Berlin, Pharmacology & Toxicology Department; 2011 to September 2016 consultant to the Department for Medicinal Products of the Federal Joint Committee (G-BA), Berlin; since October 2016 head of the Innovation Office at the BfArM, among other things.*

Status quo research & development location Germany & EU – clinical studies



Member State	Multinational Trials	
	MSC	Of which as RMS
Austria	204	36
Belgium	407	75
Bulgaria	194	2
Croatia	63	0
Cyprus	3	0
Czechia	311	63
Denmark	221	66
Estonia	41	4
Finland	86	25
France	728	118
Germany	731	224
Greece	194	2
Hungary	297	17
Iceland	4	0
Ireland	75	5
Italy	696	84
Latvia	41	3
Lithuania	52	8
Luxembourg	2	0
Netherlands	346	75
Norway	98	17
Poland	562	59
Portugal	153	7
Romania	159	7
Slovakia	114	13
Slovenia	19	2
Spain	913	251
Sweden	180	39

Quelle: EMA Homepage: Monitoring the European clinical trials environment. A deliverable of the ACT EU Priority Action 2 – February 2024

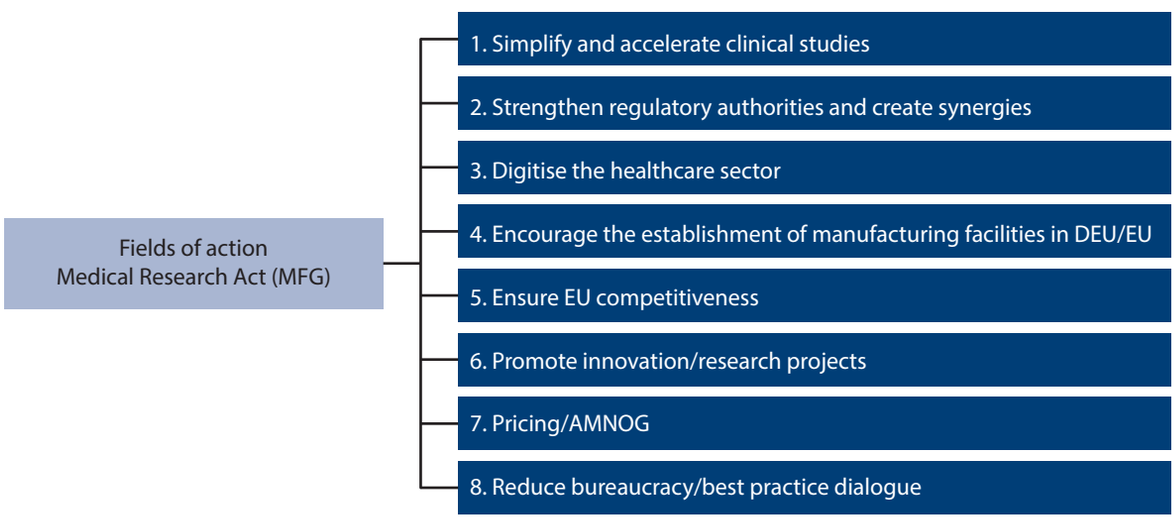
Figure 1: Germany plays a prominent role in pharmaceutical research and development, Besides Spain, most multicentre clinical studies in Europe are conducted in Germany.

on, with the MFG as the centrepiece, the notification and approval procedures under radiation protection law will be integrated into the approval procedure for clinical studies, which will significantly shorten processing times and eliminate time-consuming and cost-intensive application submissions to various authorities. The processing times for mono-national clinical studies will also be shortened.[6]

BfArM and PEI support these initiatives to facilitate clinical studies not only within the framework of the realisation and implementation of the provisions of this draft law; at the same time, BfArM and PEI are actively involved in the European measures to strengthen clinical studies in Europe („Accelerating Clinical Trials in Europe“[7]).

The BfArM and PEI welcome and are making intensive preparations for closer cooperation, in particular through the future central coordination and process management for approval procedures, consultations, and applications for clinical studies from the BfArM, as envisaged in the MFG, to speed up the processing of procedures. The two higher federal authorities are thus jointly making a significant contribution to achieving the objectives of the pharmaceutical strategy and the MFG in terms of sustainable

Pharmaceutical strategy and MFG: Overview of fields of action



Source: BfArM

Figure 2: In particular, the MFG aims to improve the legal framework for conducting clinical studies, simplify bureaucratic processes and approval procedures for clinical studies and approval programmes and facilitate access to research data.

healthcare for patients in Germany and beyond. The BfArM and PEI see themselves as enablers and drivers of modern healthcare (figure 3), not least due to their established comprehensive advisory services along the life cycle of innovative pharmaceuticals and technologies.

The MFG is closely interlinked with the Health Data Utilisation Act and the Digital Act to strengthen digitalisation in healthcare as a further factor in future viability:

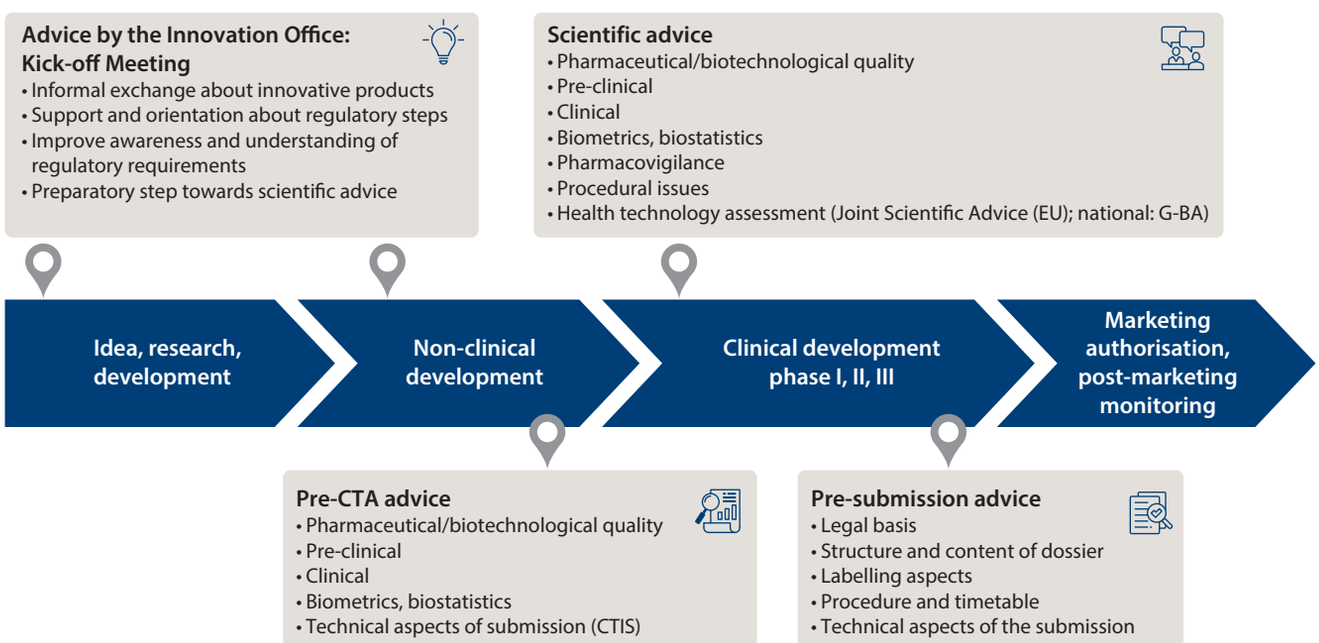
Digitalisation in healthcare and data access – further development of the Health Research Data Centre through the Health Data Use Act and the Digital Act

Digitalisation offers significant potential to revolutionise the healthcare system. It not only enables optimal care and the development of new therapies, but also efficient healthcare provision. At the core of this transformation is the intelligent and targeted use of the ever-increasing volume of health data, including so-called real-world data from medical practices and health insurance companies. This data forms an essential basis for pioneering research in the healthcare sector. The Health Research Data Centre (FDZ) at the BfArM, which is currently being set up,[8] aims to make data from patients with statutory health insurance available for research purposes, significantly improving the utilisation of real-world data. The work of the FDZ Gesundheit is embedded in the federal government's data and pharmaceutical strategy, which aims to use the opportunities of data for society.

The establishment of the FDZ Gesundheit will significantly improve the utilisation of real-world data. Access to

Regulators as enablers, not gatekeepers

The consulting portfolio along the development and complete life cycle of a product



Source: BfArM

Figure 3: The BfArM and PEI are working intensively on closer cooperation with the aim of speeding up the processing of procedures, in particular through the central coordination and procedure management for authorisation procedures, consultations and applications for clinical studies provided for in the Medical Research Act.

such data can be faster and more qualified, while safeguarding data protection aspects. In future, a wide range of billing data from all people with statutory health insurance in Germany will be available for research questions at the RDC Health, as well as data from electronic patient records. In addition to ICD-coded diagnoses and OPS-coded procedures, the FDZ Gesundheit's health insurance billing data also includes information on hospital stays, operations performed, prescribed medication, and visits to specialists (figure 4).

In addition to the potential for better care, analysing the data available at the RDC Health enables research projects to quickly identify risk factors and early warning signs of certain diseases. Through timely intervention and prevention measures, diseases can be recognised and treated at an early stage, contributing to more effective treatment outcomes and an overall improvement in healthcare. In particular, analysing large amounts of data in the RDC allows for a better understanding of individual differences in the effectiveness of treatments and medications.[9] This in-

formation on the effectiveness and safety of therapies complements the knowledge from clinical studies and can potentially contribute to improving pharmaceutical safety and the early detection of risks and side effects in the long term. This potential is also seen in the regulation of pharmaceuticals, leading to the development and publication of a corresponding strategy by the European Medicines Regulatory Network (EMRN) to strengthen the role of real-world evidence.[10] An EU-wide project, Real4Reg, is dedicated to the targeted use of large amounts of data for regulatory issues.[11]

Overall, the RDC Health creates new opportunities for medical research, improved care, and knowledge gain for the health of the population. It promotes evidence-based medicine and enables the utilisation of extensive real-world data, benefiting science, healthcare, and society as a whole.

With the Health Data Utilisation Act (GDNG)[12], the RDC is also being continuously developed. In future, authorisation to apply will be based on the purposes of use in the public interest, legally defined in the GDNG, and no longer on who submits the application. Additionally, the RDC will be able to link pseudonymised data with data from legally regulated medical registries, such as the cancer registry, if necessary for the research purpose for which the application is made and the interests of the insured persons are sufficiently safeguarded.

A central data access and coordination centre for using health data will reduce bureaucratic hurdles and facilitate access to research data. For the first time, it will be possible to link health data from various sources for research purposes. The access point will function as a central contact for data users. Data storage will continue to be decentralised, with the data remaining stored at the previous location and only being made accessible specifically for the respective research application in a secure processing environment.

The Digital Act (DigiG)[13] focuses on the digitalisation of the healthcare system and is intended to promote innovation in digital health and integrate digital approaches more deeply into healthcare processes. It includes measures such as promoting telemedical approaches, introducing e-prescriptions and electronic patient records with greater binding force, strengthening the IT infrastructure in the healthcare system, and expanding the assessment framework for digital health applications (DiGA) by the BfArM to include digital health services of higher risk classes (Class IIb).

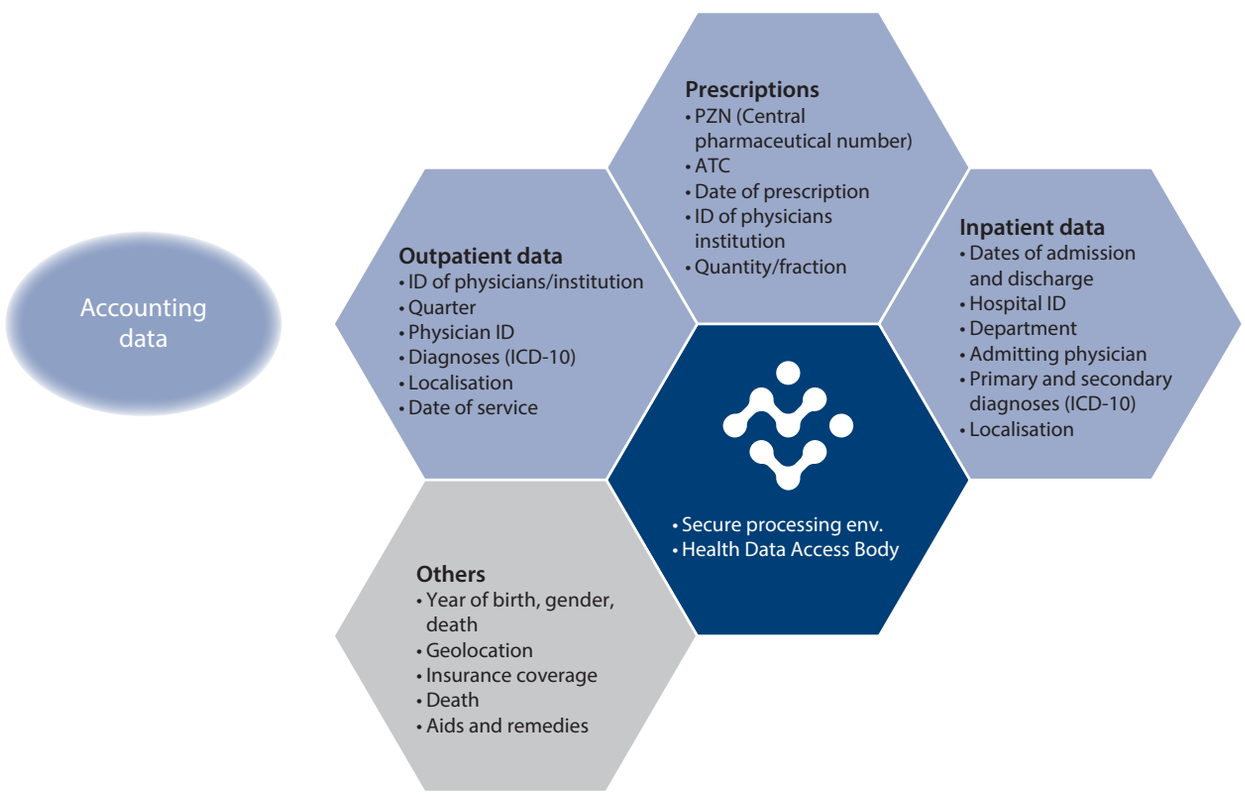
Looking to Europe: EHDS and EU-HTA create further important prerequisites for cooperation to further develop healthcare provision

In parallel to paving the way for better data availability at the national level, a regulation on creating the European Health Data Space was adopted in early March 2024. The European Health Data Network (EHDS) is a European project aimed at improving the exchange of health data between Member States to support health research and patient care. The German laws on medical research, digitalisation, and health data use are closely linked to the EHDS, as they create the legal framework required for Germany to participate in this network and enable the use of health data (secondary use) across national borders.

In preparation for the EHDS, the BfArM is involved in several projects and EU-wide initiatives (THEDaS Joint Action[14]; HealthData@Eu Pilot Project[15]; DARWIN EU[16]).

From January 2025, the new EU HTA Regulation will allow a harmonised benefit assessment - the so-called „Joint Clinical Assessment“ of the HTA institutions – of innovative medicinal products and selected medical devices to be conducted in parallel with authorisation. The associa-

Research Data Centre (FDZ) – core data set



Source: BfArM

Figure 4: In future, a wide range of billing data from all people with statutory health insurance in Germany will be available for research questions at the RDC Health, as well as data from electronic patient records.

ted objectives are faster, EU-wide access to innovative pharmaceuticals and reducing duplication of work through a centralised application instead of multiple submissions to different HTA institutions.[17]

The harmonised process of HTA assessment, already taking place in parallel with authorisation, represents an innovation that requires close coordination between the institutions responsible for authorisation and those responsible for the benefit assessment of innovative technologies.

The institutions involved are already working closely together in the implementation phase, building on the experience gained from the voluntary cooperation that has existed since 2010 in the European Network for Health Technology Assessment, EUnetHTA, and at the national level between the BfArM/PEI and the Federal Joint Committee (G-BA).

In addition to the formal implementation of the requirements of the EU HTA Regulation, the joint activities and cooperation between authorisation and HTA institutions address specific aspects such as the applicability of real-world evidence for both authorisation and HTA issues, as well as more general challenges in evidence generation for innovative approaches (along the entire life cycle of the therapeutic intervention). HTA representatives are also actively involved in the DARWIN EU Advisory Board. The authorisation and HTA authorities offer joint consultations on evidence generation regarding the requirements for both authorisation and HTA assessment. The added value of these joint consultations is generally recognised and seen by the institutions involved as an important pillar of future collaboration to support innovative development approaches.[18]

Our strategic responses to current and emerging trends and challenges – BfArM as a partner and enabler

Source: BfArM

Figure 5: The BfArM also supports and accompanies the legal initiatives through measures to identify new trends at an early stage, through the application of machine learning/artificial intelligence methods and through open dialogue with all institutions involved.

BfArM as a partner and enabler for sustainable modern healthcare

The aim of the pharmaceutical and digital strategies is to ensure a reliable supply that is fit for the future. Regarding the central measures of the laws that recently came into force based on these strategies (DiGiG and GDNG) or current draft laws (draft MFG), the BfArM has central tasks in simplifying and accelerating clinical studies and approval processes, further reducing bureaucratisation, and the future targeted use of the constantly growing volumes of health data.

The BfArM addresses these challenges – and opportunities – associated with ever faster development cycles of new technologies, as well as the implementation of these initiatives geared towards sustainable, modern healthcare as a partner. The BfArM also provides support and guidance through measures to identify new trends early and address the potential challenges associated with them, using modern technologies such as machine learning/artificial intelligence methods and open dialogue with all institutions involved in the development of innovative pharmaceuticals and medical devices (figure 5).

References

[1] EMA website: Monitoring the European clinical trials environment. A deliverable of the ACT EU Priority Action 2 – February 2024; https://go.sn.pub/3w0twq, accessed on 26 March 2024

[2] Study Pharmaceutical innovation location Germany, vfa and kearney, © 2023, https://go.sn.pub/2wi27z, accessed on 8 May 2024

[3] Pharma strategy, https://go.sn.pub/csrx81

[4] Digitalisation strategy, accessed on 1 May 2024 https://go.sn.pub/kvevj2,

[5] Draft Medical Research Act, https://go.sn.pub/12nc4m, accessed on 1 May 2024

[6] https://go.sn.pub/csrx81, , accessed on 1 May 2024

[7] https://go.sn.pub/gtcftr,

[8] https://go.sn.pub/u3jc62, accessed on 3 May 2024

[9] Ludwig M, Schneider K, Heß S et al. Aufbau des neuen „Forschungsdatenzentrums Gesundheit" zur Datenbereitstellung für die Wissenschaft. (Establishment of the new „Health Research Data Centre" to provide data for science) Bundesgesundheitsbl 67, 131-138 (2024). https://doi.org/10.1007/s00103-023-03831-z

[10] Arlett P, Kjaer J, Broich K, Cooke E (2022) Real-world evidence in EU medicines regulation: enabling use and establishing value. Clin Pharmacol Ther 111(1):21-23. https://doi.org/10.1002/cpt.2479; Reference 11 – EMRN Strategy; https://go.sn.pub/kmtub5

[11] https://www.real4reg.eu/, last accessed on 3 May 2024

[12] https://go.sn.pub/y0oyhh

[13] https://go.sn.pub/w6f449

[14] https://tehdas.eu/

[15] https://ehds2pilot.eu/

[16] https://www.darwin-eu.org/

[17]https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32021R2282

[18] Regulatory, HTA and payer interactions and collaborations: optimising their use and outcome success, CIRS workshop 10-11 March 2021; https://cirsci.org/wp-content/uploads/dlm_uploads/2022/01/CIRS-March-2021--workshop-report-Interactions-and-collaborations.pdf

Interjection - the perspective of the KBV

Dr Florian Jantschak | Department of Pharmaceuticals at the National Association of Statutory Health Insurance Physicians (KBV)

The regulations introduced with the GKV-FinStG on the guidelines for reimbursement negotiations lead to a devaluation of the minor and non-quantifiable additional benefit. Negative effects on the availability of pharmaceutical innovations are to be expected, particularly in case of combination therapies. To avoid a discrepancy between the upcoming EU HTA procedure and the AMNOG procedure, the demand for additional national analyses should be kept to an absolute minimum.

Particularly, if supplementary analyses are regularly conducted on most study data, the idea of a common European HTA procedure is undermined. The deadlines for the preparation of a manufacturer's dossier provided for in the draft implementing regulation for the EU HTA procedure appear to be too short. It is also incomprehensible that the EU HTA report can contain confidential data. Therefore, for reasons of transparency, it should be published in full.

Guidelines for reimbursement amount negotiations

Even if the medical profession is not directly affected by the new guidelines for reimbursement negotiations in Section 130b (3) SGB V, it seems necessary to point out potential collateral damage with negative effects on the availability of pharmaceutical innovations.

If the G-BA has determined a non-quantifiable or minor additional benefit for a pharmaceutical during the benefit assessment and a pharmaceutical with patent or dossier protection has been determined as appropriate comparative therapy (ACT), a reimbursement amount must be agreed that does not result in higher annual treatment costs than the ACT.

This invalidated a previously established principle of the AMNOG procedure, according to which a pharmaceutical company could claim a price premium in relation to the ACT with an active substance or combination of active substances and proven patient-relevant benefits, which was freely negotiated considering the additional benefit achieved.

For this reason, Section 5 (7) of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) already stipulated specific minimum requirements for effect sizes for the individual benefit categories as part of the original AMNOG procedure: A minor additional benefit is only present if „a moderate and not merely minor improvement" is achieved as compared to the ACT that has not previously been achieved. These minimum requirements can also be found in the IQWiG methods paper, which defines threshold values for the individual benefit categories at outcome level.[1] A non-quantifiable additional benefit is at least a minor additional benefit, but also includes the benefit categories „considerable" and „significant". Based

on the available evidence, only the categorisation of the additional benefit, which is, however, not questioned in principle, is unclear.

The GKV-FinStG thus devalued pharmaceutical innovations with minor or non-quantifiable additional medical benefit.

The consequences could be serious in hardship cases in which an active substance A with patent or dossier protection is newly authorised in combination with another active substance B without property rights and active substance A was simultaneously designated as ACT. Even if the G-BA establishes an indication of a minor additional benefit (a randomised controlled trial with high result reliability is available), a price reduction by the costs of combination partner B must be enforced to comply with the legal requirements for reimbursement amount negotiations.

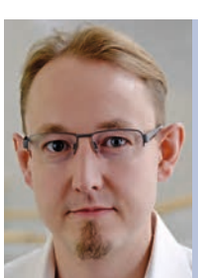
If authorisation is granted for an active substance A with patent or dossier protection that is combined with another active substance C with patent protection or dossier protection – with active substance C also representing the ACT – the new active substance A would have to be made available to the statutory healthcare system free of charge if there is an indication of a minor additional benefit . As the combination discount of 20% of the sales price must also be paid according to Section 130e SGB V, the combination could result in lower overall costs than monotherapy with a poor effect on patient-relevant endpoints. In Germany, the use of the new active substance A would thus have to be subsidised by the pharmaceutical company.

A market withdrawal by the pharmaceutical company in the described scenarios is to be expected.

Update on the EU HTA procedure

The EU HTA Regulation (Regulation (EU) 2021/2282) came into force on 11 January 2022. A phased implementation is planned. Initially, from 12 January 2025, a joint clinical assessment (JCA) will be carried out for pharmaceuticals with new active substances for the treatment of oncological diseases and ATMPs (Advanced Therapy Medicinal Products) for which an application for marketing authorisation is submitted to the European Medicines Agency (EMA) from this date. Orphan drugs may also already be included in this, although a general assessment of orphan drugs is not planned until 13 January 2028.

For Germany, representatives of the Ministry of Health, the G-BA, and IQWiG were appointed as members of the Coordination Group. In addition, the G-BA has assumed



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the chairmanship of the subgroup for joint scientific consultations (JSC subgroup). The G-BA is also represented in the other three subgroups of the JSC. To establish this involvement and future assessor activities on a solid legal basis, a legal framework in the SGB V should be created promptly to integrate the G-BA into the structures and processes of the EU HTA procedure.

Although only a few months remain until the start of the first JCAs, there is more time for the national implementation, especially for interface management between the EU HTA procedure and the AMNOG system, as the first active substance candidates are not expected to be approved and placed on the market in Germany until 2026

With reference to an answer from the Federal Government to a brief enquiry from the CDU/CSU parliamentary group in the Bundestag, it can be assumed that essential parts of the established and proven AMNOG process will remain in place.[2] However, the composition of the body of evidence on which the benefit assessment according to Section 35a SGB V will be based in future will change. Instead of a full dossier consisting of extensive data submissions in five modules, the EU HTA report will have to be considered in future. According to Article 9 (1) of the EU HTA Regulation, this report may not contain any value judgements or conclusions on the overall clinical additional benefit and should contain an aggregated presentation of the outcome parameters required by the individual member states for each PICO scheme.[3]

The German PICO scheme will not be recognisable as such in the EU HTA report and, in case of subpopulations, could also be distributed across several PICO schemes in the consolidated assessment scope. The EU HTA report can thus be regarded as a comprehensive technical and non-evaluative preliminary product that requires additional processing and is per se unsuitable for a statement or discussion in the committees of the G-BA. The IQWiG should be commissioned for this purpose, especially to extract the data relevant for the national context. For orphan drugs, the G-BA's Medical Advisory Service could take on this task like in the current procedure.

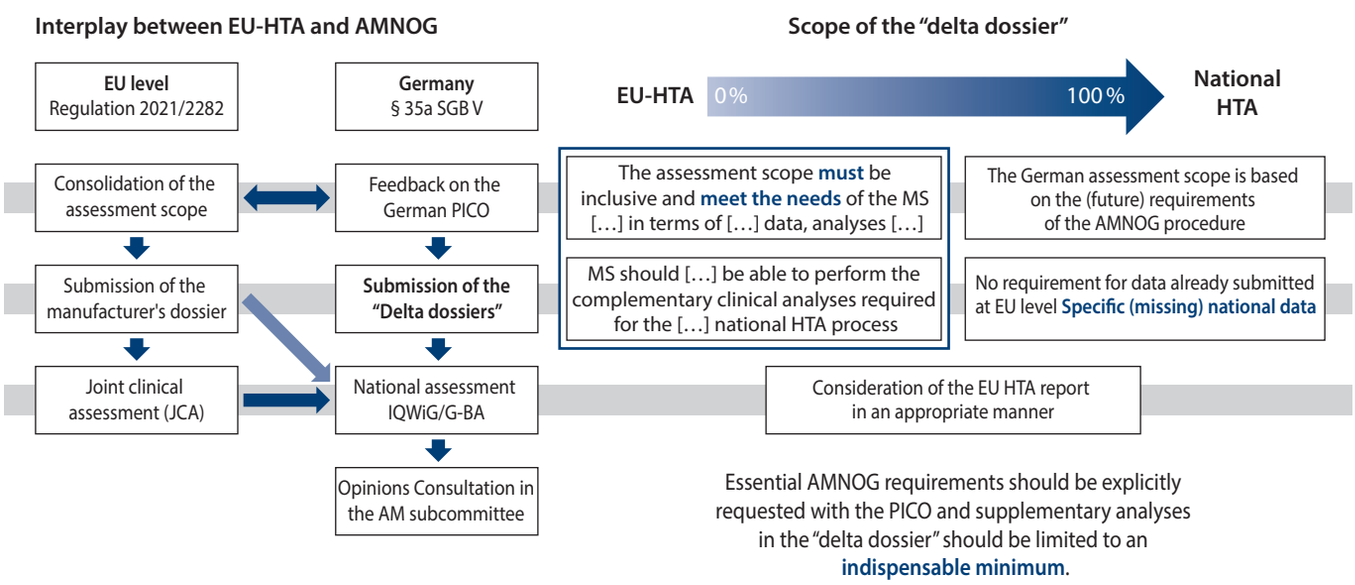
According to the EU HTA Regulation, member states can carry out supplementary clinical analyses if these are required for the national HTA process. These supplementary analyses and other information required for the AMNOG procedure (patient numbers and therapy costs) form the basis for a „delta dossier", which, in addition to the EU HTA report, will become part of the body of evidence for a benefit assessment following implementation of the EU HTA procedure. Based on this, IQWiG can then make a proposal on the extent and probability of the additional benefit in a summarised report, which then forms the basis for a hearing procedure and further consultations in the G-BA.

The content and scope of a „delta dossier" are currently being discussed but can only be finalised and defined once the methodological and procedural guidelines have been published.

However, the supplementary additional requirements should be kept to an absolute minimum to avoid a discrepancy between the EU HTA and the national procedure. The more supplementary analyses are required with the „delta dossier", the more the idea of a joint clinical assessment is undermined, creating a contradiction to the purpose of the EU HTA Regulation, especially if supplementary analyses are routinely conducted on a large portion of the study data (figure 1).

According to Article 8(6) of the EU HTA Regulation, the scope of the assessment of the procedure must be inclusive and meet the needs of the member states regarding the information, data, and analyses to be submitted by the MAH. The Practical Guideline on the scoping process speci-

Possible discrepancy between EU HTA and AMNOG procedure



Source: Interjection – the perspective of the KBV | Interdisciplinary Platform on Benefit Assessment 15 March 2024

Figure 1: The more supplementary analyses are demanded by the member states during their national HTA processes, the more they move away from the idea of a joint clinical assessment.

fies that it is the responsibility of the member states to ensure this with their respective PICO, which is to be defined in accordance with national legislation and procedures.[3]

If the G-BA cannot use the EU HTA report, the PICO has therefore been defined incorrectly or with insufficient precision. Essential components of the AMNOG requirements, particularly the underlying methodology, would therefore have to be explicitly required in the PICO if the corresponding guideline opens up this possibility or at least does not exclude it. An example of this is the 15% threshold proposed by IQWiG and accepted by the G-BA for the recognition of responder analyses.[4] In order to reduce the number of PICOs and outcome parameters to be processed, an exchange between the assessors and the respective member states is planned for PICO consolidation. The definition of the scope of the assessment is currently being tested and refined through practice procedures (Mock PICOs).

Draft implementing regulation for the EU HTA procedure

The draft implementing regulation for the EU HTA procedure was published on the EU Commission's website on 5 March 2024 and was open for public comment until 2 April 2024.[5] The following issues were criticised by the KBV:

Even assuming that the number of PICOs to be proces-

sed can be reduced as part of the consolidation process, a period of 90 days (only 60 days in an accelerated procedure) for the preparation of an EU dossier by the company appears to be too short.

It is recommendable that current data from clinical studies can be submitted and considered during an ongoing JCA. However, based on the existing deadlines and high number of necessary analyses, the practical feasibility of this option is doubted.

The EU HTA report contains the scientific analysis and presentation of aggregated data from the company's dossier, considering the specific needs of the individual member states. It is incomprehensible that the EU HTA report can contain confidential data. Therefore, for reasons of transparency, it should be published in full.

References

[1] Institute for Quality and Efficiency in Healthcare (IQWiG) (2023). General Methods Version 7.0. https://go.sn.pub/mkwigq

[2] Response of the Federal Government to the minor interpellation of the CDU/CSU parliamentary group - printed matter 20/6665 – National implementation of the European health technology assessment process, printed matter 20/6930. (22 May 2023). https://go.sn.pub/0cyt81

[3] EUnetHTA 21 (2023). Practical Guideline D4.2 Scoping Process Version 1.1. https://go.sn.pub/a4zemy

[4] Institute for Quality and Efficiency in Healthcare (IQWiG). „Clinical relevance of patient-reported outcomes: New threshold proves fit for practice." (Press release from 18 February 2021). https://go.sn.pub/jmstw4

[5] Draft implementing regulation laying down procedural rules for the preparation of joint clinical assessments of medicinal products for human use, Ares (2024)1703728. (5 March 2024).

A review of the internet sources was carried out on 8 April 2024.

Demanding and promoting authorisation, HTA, and reimbursement: theses on further development

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In recent years, the spectrum of pharmaceutical innovation has changed significantly, bringing with it new opportunities and challenges. In this context, different evidence requirements for pharmaceutical authorisation, benefit assessment, and reimbursement decisions are critically reflected upon. It is discussed whether harmonisation of these requirements is actually desirable and feasible given the different responsibilities. This article emphasises the need for a differentiated view of the evidence situation in special therapeutic situations and close cooperation between companies, regulatory authorities and HTA institutions to ensure the best possible access to innovative pharmaceuticals.

Pharmaceutical innovation in transition: significant challenges for marketing authorisation and benefit assessment

The spectrum of pharmaceutical innovation has changed significantly in recent years. This brings new opportunities but also challenges for pharmaceutical development, authorisation, and reimbursement decisions:

- A better understanding of disease processes enables the development of new, more targeted therapeutic approaches.
- Innovations for very small patient groups, for which there is often only limited evidence at the time of authorisation, also because RCTs are not always feasible for practical and ethical reasons
- Biomarker-specific therapies are playing an increasingly important role and are dependent on diagnostics (precision medicine) and other technologies (integrated solutions).
- Increasing use of adaptive study designs, single-arm clinical studies, and intermediate and surrogate endpoints.
- Accelerated transition to a life cycle approach in evidence generation and authorisation.
- Rapid development of medical standards and the associated challenges for the design of comparative clinical studies.

There is a different dynamic in the USA and Europe regarding the approval and availability of innovative pharmaceuticals. For example, 113 of the pharmaceuticals approved for the first time in the USA between 2019 and 2023 were not available in the five largest European markets (Germany, France, Spain, Italy, UK) in January 2024 (regardless of reimbursement status). Conversely, only 11 of the pharmaceuticals authorised in the EU4/UK between 2019

and 2023 were not yet available in the USA in January 2024 (IQVIA Institute 2024). Looking at all 460 new pharmaceuticals launched in OECD member states between 2012 and 2023, 85 per cent were launched in the USA and only 61 per cent in Germany, which is still well above the average for OECD member states (PhRMA 2023).

On the one hand, this development is due to the increased use of special authorisation procedures in the USA. On the other hand, the fragmentation and complexity of national reimbursement hurdles lead to significantly higher expenditure of time and resources for pharmaceutical companies. This complexity leads to significant uncertainties about the ultimate availability for patients and the resulting economic success for pharmaceutical companies.

The increasing understanding of disease processes, new methods of pharmaceutical development, the rapidly increasing availability of relevant healthcare data, but also changing social expectations, have led to corresponding adjustments, additions, and further developments in the regulation of pharmaceuticals (EMA 2020, FDA 2022). Authorisation procedures adapted to the specific medical context should ensure that urgently needed pharmaceuticals can be made available to patients without delay.

Such options are used in special therapeutic situations to fulfil society's expectation of providing patients with serious or life-threatening diseases with earlier access to novel pharmaceuticals with recognisably positive risk-benefit potential (Eichler, Sweeney 2018). In this way, the EU authorisation system, also with the significant involvement of the German regulatory authorities, has so far succeeded in promoting the timely supply of safe, innovative pharmaceuticals in special therapeutic situations (EMA 2017).

At the same time, further developed regulatory authorisation procedures and methodologies and the resulting changes in the evidence situation at the time of authorisation are also fuelling the discussion about evidence requirements for HTA between regulatory authorities, HTA institutions, and payers. Innovative approaches on the approval side are increasingly being openly criticised, which is directly or indirectly accompanied by demands to adapt approval practice (Wieseler, McGauran, Kaiser 2019). The different roles and responsibilities of authorisation decisions and benefit assessments and their institutional independence appear to be partially overlooked.

Regulatory innovation requires constructive responses in benefit assessments

Implications of further developments of upstream authorisation processes for downstream HTA and reimbursement processes and their further development must be systema-

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tically evaluated and, if necessary, lead to downstream modifications of benefit assessment and reimbursement procedures. Without these modifications, there is a risk that the healthcare benefits for patients intended by the regulatory innovation cannot be realised.

Of particular importance in the context of benefit assessments is a stronger reference to evidence requirements in special therapeutic situations and the consideration of resulting limitations for the generation of clinical evidence. Therapeutic situations are considered special if they do not allow studies of the highest evidence level to be conducted for practical or ethical reasons. Such considerations are made on a case-by-case basis as part of the authorisation process, considering the type, severity, and rarity of the disease.

Due to the assessment practice in the AMNOG procedure, an additional benefit is only recognised in rare exceptional cases if the approval is based on a non-randomised study. Here, the benefit assessment should be supplemented to ensure that special features of the therapeutic context that have prevented the submission of evidence of the highest level (RCT) (unmet medical need, severity of the disease and, in particular, the size of the target population) are systematically taken into account (vfa 2023). If it was not appropriate to provide evidence of the theoretically highest level in view of the therapeutic context, it seems disproportionate to nevertheless demand the maximum standard of evidence (Hebborn 2019). At the same time, it should be jointly defined how the best available evidence at the time of the benefit assessment can be used.

Dealing with evidence expectations in authorisation and reimbursement

Different responsibilities and the necessarily different decision-making calculations of authorisation („benefit-risk“) and reimbursement decisions („opportunity costs“) can lead to a different assessment of uncertainty about treatment outcomes and measures to reduce them. Different evidence expectations of the institutions involved in authorisation and reimbursement are ultimately a consequence of these different responsibilities. Efforts to fully harmonise the evidence requirements of both processes without reference to their different responsibilities therefore do not appear to be appropriate.

Nevertheless, benefit assessments and reimbursement decisions must refer to previous authorisation decisions. It is thus essential that those involved in the benefit assessment and those responsible for reimbursement decisions are able to understand the assessment of the therapeutic context made in the authorisation decision. However, this does not justify a complete harmonisation of the evidence requirements. There is also a lack of congruence between the current and future patient populations affected by European marketing authorisation decisions and the population groups affected by temporary reimbursement decisions within the framework of the German statutory healthcare system and comparable security systems in other member states. As can be seen from the introductory provisions of the EU HTA Regulation (2021/2282), the parties involved in the legislation also lacked the fundamental willingness to systematically harmonise evidence expectations of the HTA processes (Recital 15). At the same time, there is a lack of political will to conduct a joint appraisal of the clinical evidence situation. This is strictly reserved for national decision-makers (Recital 14).

Integrated evidence planning in corporate responsibility

The prerequisite for successful pharmaceutical development is that the pharmaceutical company addresses not

only the evidence expectations of the marketing authorisation but also those of the various national HTA institutions and payers in global development programmes in the best possible way. In the area of conflict between marketing authorisation and HTA/benefit assessment, companies are therefore faced with the question of how they should map the sometimes differing evidence requirements of marketing authorisation and benefit assessment in their development plans for innovative pharmaceutical products as a whole (CIRS 2021).

The different evidence requirements and the differences in HTA/benefit assessment and pricing practices in various countries significantly increase the complexity of this planning. Compromises are unavoidable if, given the inevitably global context, not all requirements can be realised simultaneously in development programmes.

New forms of targeted cooperation between companies, regulatory authorities, and HTA institutions are therefore of particular importance in this planning at the national level and, considering the EU-wide authorisation, also at the intergovernmental level. Of particular importance here is the early dialogue between pharmaceutical companies and HTA institutions – such as the consultation on benefit assessment in Germany by the G-BA with the involvement of the regulatory authorities or, in future, at EU level as part of the planned joint scientific consultation by the EU HTA Coordination Group with the possible involvement of the EMA. Product-specific consultations on benefit assessments can significantly increase the information base for pharmaceutical companies and lead to an improved integration of the various evidence expectations.

However, to ensure equal opportunities for pharmaceutical companies to access early advice at the European level, the available capacity on the part of the authorities involved in the EU HTA process must be increased to a considerable level. Whether this is possible is still not foreseeable at present, just a few months before the introduction of joint scientific consultations within the framework of the EU HTA Regulation.

Additional reimbursement models to address residual uncertainty in special therapy situations

In situations where the pharmaceutical company cannot provide the evidence required for an appropriate price as part of the added benefit assessment at the time of authorisation, the fundamental question arises as to whether the pharmaceutical product should be (permanently) launched in Germany at all. This is particularly problematic in situations involving pharmaceuticals that are prioritised by the regulatory authorities and whose availability is considered necessary for society as part of standard care.

In this context, the denial of any additional benefit and the expected consequences for the achievable reimbursement amount are misleading signals for desired further innovation activity. It also bears the risk of decoupling from global scientific progress in pharmaceutical development. It is important to counteract this, also by means of adaptive reimbursement models. These should make it possible to reflect the success of therapies that can be measured over the course of treatment. They can make a valuable contribution to a stronger reconciliation of society's interest in the earliest possible availability of regulatory prioritised pharmaceutical products and the interest in an economical supply of innovative pharmaceutical products (Hebborn 2019).

Conclusion

The permanently changed spectrum of innovative pharmaceuticals, associated social expectations, and new possibilities and limits for generating clinical evidence are

testing the limits of the processes and methods currently used in marketing authorisation, benefit assessment, and reimbursement. In the context of market authorisation, the reaction to this has been to further develop and supplement authorisation procedures and the evaluation methodology used in authorisation decisions. In the area of HTA benefit assessment and reimbursement, however, these developments have hardly been translated into corresponding modifications and additions to the existing regulations, methods, and reimbursement instruments.

In this context, it does not appear appropriate to strive for an alignment of evidence requirements in the authorisation with those of the downstream benefit assessment. Instead, better cooperation between companies, regulatory authorities, and HTA institutions should be developed to efficiently address the different evidence requirements.

There is an urgent need to supplement the regulatory framework for benefit assessments to ensure that restrictions on evidence generation resulting from the special characteristics of therapeutic situations can be systematically reflected and addressed. Moreover, the introduction and targeted use of adaptive reimbursement models can help to better account for the evidence situation and uncertainty in particular therapeutic situations and effectively create incentives their reduction.

References

[1] CIRS (2021): Regulatory, HTA, and payer interactions and collaborations: optimising their use and outcomes success. 10-11 March 2021. Workshop Report. https://go.sn.pub/obhbr5

[2] Eichler HG, Sweeney F (2018): The evolution of clinical trials: Can we address the challenges of the future? Clinical Trials, 15 (S1), 27-32.

[3] EMA (2017): Conditional marketing authorisation. Report on ten years of experience at the European Medicines Agency. https://go.sn.pub/fhc6fq

[4] EMA (2020): EMA Regulatory Science to 2025. Strategic reflection. https://go.sn.pub/y5khcl

[5] FDA (2022): Advancing Regulatory Science at FDA: Focus Areas of regulatory science (FARS). https://go.sn.pub/3pqtjs

[6] Hebborn A (2019): Alternative Erstattungsmodelle für regulatorisch priorisierte Arzneimittel (Alternative reimbursement models for regulatory prioritised medicinal products), in: Storm A: AMNOG Report 2019. Beiträge zur Gesundheitsökonomie und Versorgungsforschung (Contributions to health economics and healthcare research) (Volume 29). https://go.sn.pub/qawa44

[7] IQVIA Institute (2024): Global trends in R&D 2024. https://go.sn.pub/w7l15s

[8] PhRMA (2023): Global access to new medicines report. https://go.sn.pub/tlhhdr

[9] Vfa (2023): AMNOG 2025. Besondere Therapiesituationen brauchen besondere Bewertung (Special therapy situations require special assessment.). https://go.sn.pub/269M2K

[10] Wieseler B, McGauran N, Kaiser T (2019): New drugs: where did we go wrong and what can we do better? BMJ. 2019 Jul 10;366:l4340. doi: 10.1136/bmj.l4340. Erratum in: BMJ. 2019 Jul 24;366:l4837. doi: 10.1136/bmj.l4837. PMID: 31292109.

Decision-making under uncertainty: consequences for JCS and HTA organisations

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The European Commission has commissioned the European Medicines Agency (EMA) and the European Network for Health Technology Assessments (EUnetHTA 21) consortium to develop an implementation plan for parallel and single scientific consultations (JSC) for applicants by EMA and HTA organisations. This article examines the differing perspectives of EMA and HTA organisations on decision-making under uncertainty (decision-making under uncertainty) for JSCs and highlights their implications for the dossier development of applicants for oncological therapies for approval and reimbursement.

Introduction

Efforts to create synergies for the authorisation of pharmaceuticals by the European Medicines Agency (EMA) and the European Network for Technology Assessment EUnetHTA, whose mandate ended in September 2023 under EUnetHTA21, have been ongoing since 2010.[1] Identified priorities for cooperation and initial results on parallel consultations (formerly Parallel Scientific Advice/Early Dialogue) for applicants of innovative products have been published in two work plans for 2012-2015 and 2017-2021.[2,3]

Following the adoption of contractual agreements on Joint Clinical Assessment of HTA activities in the EU,[4] which will come into force in 2025, the European Commission has mandated EMA and the EUnetHTA21 consortium to develop an implementation plan for the cooperation priorities identified in previous work plans. The general objectives of this cooperation include improving process efficiency and quality, respecting the remits of different decision-makers, supporting mutual understanding and dialogue on evidence needs, and facilitating patient access to new pharmaceuticals in the EU.[1]

Additionally, guidelines for the submission of applications for parallel scientific consultations on new products (Joint Scientific Consultations, JSC) for the transition period 2023 to 2025, leading up to the implementation of the pan-European Joint Clinical Assessment (JCA) by HTA organisations, have been developed.[5] During this interim period, applications are coordinated by the Federal Joint Committee (G-BA), acting as the interim HTA coordination contact.

Applications for JSC can only be submitted if the key study (pivotal clinical trial phase II or III) has not yet been initiated. Other criteria for consideration include the lack of treatment alternatives, application for a new class of medi-

cinal product, the importance of the pharmaceuticals for patients, public health, and the healthcare system, relevant possible further treatment indications, European-wide relevance, and the existence of a Europe-wide research priority.[6]

This article focuses on the planned reprocessing of a European singular process for JSCs by EMA and HTA organisations for applicants of new pharmaceuticals, addressing the needs of both EMA and HTA organisations.1 The differing perspectives of EMA and HTA organisations on dealing with uncertainty in decision-making for JSCs and their consequences for the dossier development of oncological therapies for approval and reimbursement will be examined.

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Perception of risk and benefit assessment by regulatory authorities and HTA organisations

Approval procedures for oncology products are undergoing significant changes due to the rapid development of increasingly specific and individualised therapies in oncology. An overview of all oncology products approved by the EMA in Europe and the FDA in the USA between 2015 and 2020 illustrates this trend (table 1).[7] In contrast to the EMA, the FDA approved a third and almost half of all orphan and non-orphan drug approvals using the accelerated procedure. The median time to authorisation for orphan and non-orphan drugs was significantly shorter at the FDA than at the EMA. The proportion of phase III studies was higher for EMA approvals than for FDA approvals, while significantly more pharmaceuticals with single-arm studies (non-orphan disease 43%, orphan disease 54%) without an active control arm were approved by the FDA compared to EMA (non-orphan disease 21%, orphan disease 36%). This trend towards approving oncology products without comparator arms is more pronounced in the USA than in Europe.

This raises questions about the significance and consequences of authorising pharmaceuticals from studies without comparator arms for JSCs aimed at by EMA and HTA organisations. Can synergies be developed from the different approaches to benefit assessment by regulatory authorities and HTA organisations that lead to increased assessment process efficiency?

The balance of the risk-benefit profile of new pharmaceuticals, evaluated within a structured and systematic benefit-risk framework, is crucial for regulatory authorities (figure 1).[8]

There are no universally accepted methods for deriving a risk-benefit profile or a „benefit-risk ratio“ compared to alternative treatments.[8] The CIOMS (Council for Internatio-

Characteristics of studies for the approval of oncology products by the EMA and FDA from 2015 to 2020

	EMA Non-orphan drugs n = 38	**EMA** Orphan drugs n = 28	**FDA** Non-orphan drugs n = 35	**FDA** Orphan drugs n = 35
Type of approval				
Conditional	2 (5%)	9 (32%)	N/A	N/A
Accelerated	N/A	N/A	11 (31%)	16 (46%)
Standard	36 (95%)	19 (68%)	24 (69%)	19 (54%)
Duration of assessment (days) Median (Q1, Q3)	364 (330, 419)	333 (238, 422)	193 (149, 243)	203 (159, 242)
Last development phase				
Phase I	1 (3%)	1 (4%)	1 (3%)	2 (6%)
Phase II	8 (21%)	13 (46%)	11 (31%)	18 (51%)
Phase III	29 (76%)	14 (50%)	23 (66%)	15 (43%)
Single-arm	8 (21%)	10 (36%)	15 (43%)	19 (54%)
Multi-arm open-label	14 (37%)	15 (54%)	7 (20%)	11 (31%)
Multi-arm blind	16 (42%)	3 (11%)	13 (37%)	5 (14%)
Comparator arm of the approval study				
None (single arm)	8 (21%)	10 (36%)	15 (43%)	18 (51%)
Placebo	11 (29%)	5 (18%)	10 (29%)	6 (17%)
Standard of care	7 (18%)	7 (25%)	1 (3%)	3 (9%)
Active comparator arm	12 (32%)	6 (21%)	9 (26%)	8 (23%)

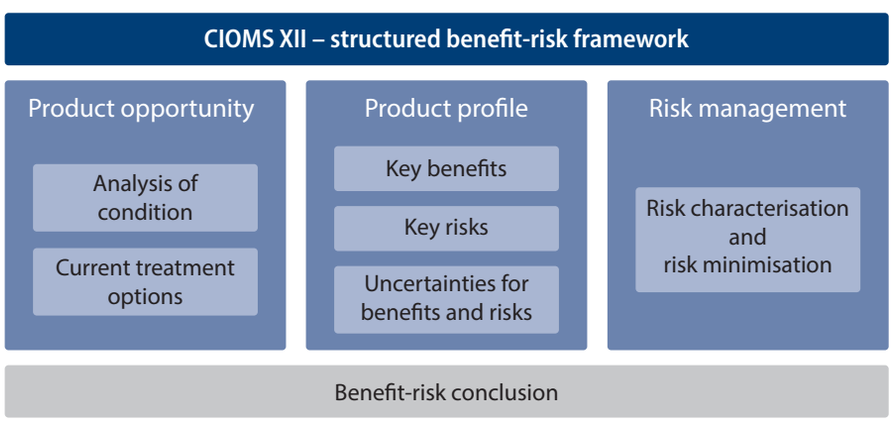
Source: adapted from [7]

Table 1: In contrast to the EMA, the FDA approved a third and almost half of all orphan and non-orphan drug approvals using the accelerated procedure.

nal Organisations of Medical Sciences) report describes various instruments for risk-benefit assessment such as PrOACT-URL (Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainties, Risk attitudes/risk tolerance, Linked decisions).

The FDA, on the other hand, focuses on various dimensi-

Benefit-risk structure for the approval assessment of pharmaceuticals under review Council for International Organizations of Medical Sciences (CIOMS)



Source: [8]

Figure 1: Regulatory authorities focus on the balance of the risk-benefit profile of new pharmaceuticals. The FDA focuses more on different dimensions of the benefit-risk analysis to be considered.

ons of the benefit-risk analysis to be considered, which are roughly congruent with the CIOMS proposal for risk-benefit assessment. The risk-benefit assessment considers all available evidence (totality of evidence), which includes the context of the treatment options, the evidence on benefit and risk, uncertainty of the data situation and the options for risk minimisation and risk management. Interestingly, EMA avoids the terms „benefit" and „risk" – referring to the CIOMS working group report – arguing that „there is no standard or widely accepted definition of the terms „benefit" and „risk" in medicine or specifically for pharmaceuticals".[9] It therefore uses the terms „favourable effects" and „uncertainty about favourable effects", and „unfavourable effects" and „uncertainty about unfavourable effects".[9]

A systematic analysis by EMA concludes that qualitative assessment of the risk-benefit is sufficient in most cases. Quantitative models require a qualitative framework, and most quantitative decision models are unsuitable for authorisation procedures. EMA considers only three quantitative approaches to be sufficiently comprehensive, which represent a numerical risk-benefit balance and allow utility values for desirable and undesirable effects with associated probabilities for the uncertainty of the effects: Bayesian statistics, decision trees and influence/relevance diagrams, and multi-criteria decision analysis (MCDA).[9] It is thus not surprising that Pinto et al. did not find a single quantitative benefit-risk assessment in their systematic analysis of 66 and 70 positively assessed applications for the approval of oncology products between 2015 and 2020 by the EMA and the FDA, respectively.7

In contrast, HTA is defined as a scientific evidence-based

process for assessing the relative effectiveness of new or existing medical technologies.[4] HTA focuses on the value, safety, and cost-effectiveness of new technologies compared to a standard, aiming to quantify the additional benefit. The risk perception of HTA organisations focuses on the decision uncertainty regarding the effectiveness and safety of new technologies or interventions compared to current clinical practice (comparative therapy), as well as financial and expected healthcare system consequences.[10]

This approach is reflected e.g. in the assessment of AMNOG benefit dossiers by the G-BA. In 62 AMNOG procedures involving 52 active substances and 111 indirect comparisons, in the absence of randomised evidence, health insurance coverage was denied in 94% of applications due to an unquantifiable additional benefit.[11] Similarly, for HTA organisations, the totality of evidence is not a viable concept because it would include non-randomised evidence in the spirit of the best available evidence, and many HTA organisations do not incorporate cost-effectiveness analyses into their benefit assessments, or do so only to a limited extent.

Deciding under uncertainty

Uncertainty in favourable and unfavourable effects assessment[9] is a key issue for regulatory authorities when assessing pharmaceuticals. Adequate trial design, study methodology, and sufficient data can reduce many sources of uncertainty. The therapeutic context, lack of treatment options, and disease severity and frequency can influence the acceptance of uncertainty.

Acceptance of uncertainty varies depending on whether it concerns a rare, prognostically unfavourable tumour disease with limited treatment options or a primary preventive therapy targeting a high-prevalence risk factor.[12] Decision-making under uncertainty involves different criteria for regulatory authorities and HTA organisations.

An international and interdisciplinary HTAi-DIA Working Group has published considerations for systematically identifying and reducing uncertainty in the HTA decision-making process and has attempted to identify various aspects of uncertainty.[13] The working group identified 19 different definitions of uncertainty but could not reach a consensus on a comprehensive definition applicable to HTA regulation. In a next step, they summarised 12 aspects of uncertainty into blocks for identifying relevant uncertainty in decision-making: „unavailable", „inaccurate", „conflicting", „not understandable", „random variation", „information", „prediction", „impact", „risk", „relevance", „context", and „judgement". One block comprises parametric, epistemic, and structured forms of uncertainty, which are determined by unavailable, biased, contradictory, or unclassifiable information. Another block includes risk aspects of decision-making, as well as the assessment of the impact of certain decisions (or their alternatives) in the future. A third block contains contextual aspects of decision-making that are subject to uncertainty.

The HTAi-DIA Working Group's approach lacks sufficient systematisation and theoretical foundation. Djulbegovic et al.[14] present a systematic classification of uncertainty that makes it easier to capture the fundamental dimensions of uncertainty in medicine. They describe four basic dimensions: Epistemic uncertainty (including measurement, systematic and random error, natural variation, application of probabilities to individual cases), subjective uncertainty (includes lack of or excess information, conflicting evidence, extent of belief, values and preferences, and disagreement), decision model uncertainty, and linguistic uncertainty (numerical vagueness, ambiguity, dependence on context, lack of specificity and determinacy). Key differences in the conceptualising uncertainty between regulatory authorities and HTA organisations will be briefly explained.

The subjective dimension of uncertainty in the decision-making processes of regulatory authorities and HTA organisations differs in the extent of beliefs, values, and preferences. In the risk-benefit determination, in the sense of a risk-risk trade-off,15 regulatory authorities compare the risk of not treating a condition or treating it with a current standard therapy with the risk of treating the condition with a new therapy (figure 2).[15] In oncology approval decisions, regulators are more willing to take risks due to unmet needs, disease severity, and limited treatment options. This is illustrated by the increase in approvals through single arm phase II-III-studies generating evidence in a therapeutic setting incompatible with equipoise.[16]

In contrast, HTA organisations are more risk-averse focusing on quantifiable additional benefits compared to an accepted standard and minimising harm from side effects. Risk aversion and a shift to the right in figure 3, beyond the maximum point for efficiency, increases the need for data with increasing risk aversion, which drives up research costs and opportunity costs. HTA organisations assume equipoise, i.e. maximum uncertainty regarding the relative therapeutic effect of an index treatment compared to alternative treatments.[16] In this context, according to Djulbegovic, equipoise has a „very specific interpretation with regard to equivalent assumptions or uncertainties about the relative therapeutic effects of alternative treatments",[16] which, for regulatory authorities, are not primarily decisive given the increasing number of new and individualised treatment methods in oncology.

It can also be concluded from the above that the decision-making process of approval procedures of regulatory and HTA organisations should be understood as context-specific processes that extend over the entire lifespan of a pharmaceutical and, according to Djulbegovic et al. can be assigned to linguistic uncertainty. Probability theories for quantifying and minimising uncertainty contribute to decision-making, but represent only one – albeit important – aspect of (epistemic) uncertainty.[17,14] The causes of uncertainty influence the flow of information between the system or phenomenon being analysed or observed, which „generates" uncertainty, and the choice of model for the taxonomy of uncertainty.[17] However, standardisation of the processes of approval and HTA organisation for JSC can only be successful if the differences in the contextuality of uncertainty and the taxonomy of uncertainty are made explicit for the respective stakeholders.

What does this mean for the JSC process for oncology products? In order to make an assessment, some further information on the newly planned administrative processes of the JSC process is required in advance. During the transition period 2023 to 2025, an applicant can only obtain a consultation if two HTA organisations from member states express interest in an application. The role of the two HTA organisations involved remains open and ranges from active participation or consultation on purely national criteria for the authorisation process to an observer status that leaves all consultation steps to the second HTA organisation involved.

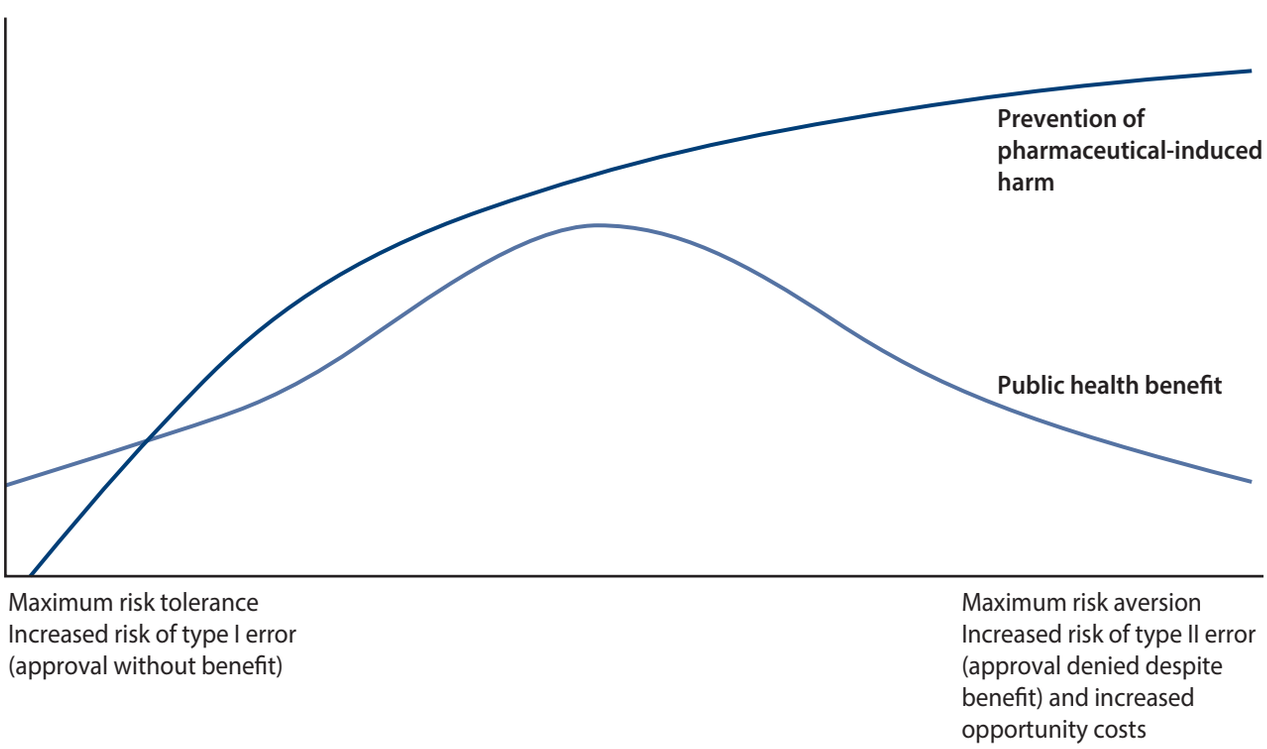
The applicant cannot choose the HTA organisation. In addition, consultation for advice on market authorisation, remuneration and evidence generation after authorisation is only possible if the applicant discusses the authorisation study design simultaneously. This procedure involves considerable and sometimes additional uncertainties for the applicant compared to the previous models of parallel consultation, as the applicant is in consultation with two different HTA organisations with possibly divergent views at the same time.

The JSC focuses on individual points of the PICO questionnaire. Uncertainties regarding the intervention

can arise, particularly in case of therapies that are highly specific to a certain patient subgroup or those that are administered in combination with another therapeutic agent. The ability of HTA organisations to influence the design of the pivotal study carries with it the additional risk, in addition to the technical organisational issues regarding the possibility of randomised comparisons, of difficult to reconcile differences between stakeholders in risk acceptance and in dealing with uncertainty in decision-making processes. It must be assumed that HTA organisations are predominantly opposed to single-arm phase II/III studies and are technically challenged to formulate acceptable methods of indirect comparisons based on external controls and to allow them in HTA dossiers.

The involvement of two HTA organisations can lead to divergent views on comparator treatments. Validated surrogate markers may enable conditional approval for regulatory authorities, but HTA organisations may consider

Public health benefits versus risk aversion in the approval of pharmaceuticals



Source: [15]

Figure 2: The subjective dimension of uncertainty in the decision-making processes of regulatory authorities and HTA organisations differs in the extent of beliefs, values, and preferences.

them of secondary importance, affecting consultation on approval study design. This in turn has a significant impact on the consultation and discussion on the planning and design of the relevant approval study. A further important point of the JSC is the handling of additional information gain between the design and conduct of the pivotal approval study and questions of adequate control comparisons.

For example, a randomised phase III study may no longer contain the best available comparator treatment at the time of the reimbursement application due to parallel treatment progress and may therefore be rejected as only conditionally relevant in the HTA procedure. Concepts for dealing with uncertainty in the consultation phase of regulatory authorities and HTA organisations in this specific situation are imperative, as it can be assumed that the scenario described will occur more and more frequently.

Conclusions

At the current stage of the JSC development, applicants must expect additional uncertainties and extended preparation times for the consultation and approval process.

The JSC process's fundamental problem is the inadequate description of contextual perspectives and decision-making processes under uncertainty by regulatory authorities and HTA organisations. Standardising the process will represent progress only if it releases synergies, saves resources and, in particular, saves time. Fears at the current planning stage that JSC only creates limited information gains and planning certainty for applicants but can be associated with additional work and loss of time, are not unfounded.

How risk is dealt with and the willingness to accept risk is also determined by society. It is perfectly understandable that the willingness to take risks and the perception of risk on the part of patients, particularly in the case of serious illnesses, is different from that of those treating patients, regulatory authorities, or the public. Healthcare decision-makers should be aware that decision-making under uncertainty is part of everyday life in clinical medicine. Uncertainty in clinical medicine is experiential and, when characterised by self-reflection and a lifelong willingness to learn, can be described as what might be termed the „art of healing". Moreover, uncertainty also determines a pattern of success in medicine and drives new clinical insights.[15]

Reverences

[1] Agency EM. Priority topics for European collaboration between regulators and health technology assessment bodies. 6 April 2021.

[2] Cooperation between regulators and HTA bodies creates synergies [press release]. 14 April 2016.

[3] Report on the implementation of the EMA-EUnetHTA work plan 2017-2021. 2021. https://go.sn.pub/4tp3dj. Accessed 1 March 2024.

[4] European Health and Digital Executive Agency (HaDEA) HA-EHSF. Service Contract for the Provision of Joint Health Technology Assessment (HTA) Work Supporting the Continuation of EU Cooperation on HTA. In: 16 September 2021.

[5] Agency EM. Rybrevant; CHMP assessment report [online. https://wwwemaeuropaeu/documents/assessment-report/rybrevant-epar-public-assessment-report_enpdf 2021.

[6] Guidance on Parallel EMA/EUnetHTA 21 Joint Scientific Consultation. 6 September 2024. https://go.sn.pub/j6rkjp. Accessed 1 March 2024.

[7] Pinto CA, Balantac Z, Mt-Isa S, et al. Regulatory benefit-risk assessment of oncology drugs: A systematic review of FDA and EMA approvals. * Drug Discov Today. 2023;28(10):103719.

[8] report CfIOoMSCWG. Benefit-risk balance for medicinal products (draft report). Geneva Switzerland, 12 June 2023.

[9] Benefit-risk methodology project Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment 31 August 2010. https://go.sn.pub/q2vg9b. Accessed 1 March 2024.

[10] Grimm SE, Strong M, Brennan A, Wailoo AJ. The HTA Risk Analysis Chart: Visualising the Need for and Potential Value of Managed Entry Agreements in Health Technology Assessment. Pharmacoeconomics. 2017;35(12):1287-1296.

[11] Werner S, Lechterbeck L, Rasch A, Merkesdal S, Ruof J. Untersuchung der Akzeptanz und der Ablehnungsgründe indirekter Vergleiche in IQWiG-Nutzenbewertungen (Investigation of the acceptance and reasons for rejection

of indirect comparisons in IQWiG benefit assessments). Gesundheitsökonomie & Qualitätsmanagement 2020;25((01)):24-36.

[12] Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (CBER) Center for Drug Evaluation and Research (CDER) October 2023. https://go.sn.pub/qxhi1p. Accessed 1 March 2024.

[13] Hogervorst MA, Vreman R, Heikkinen I, et al. Uncertainty management in regulatory and health technology assessment decision-making on drugs: guidance of the HTAi-DIA Working Group. Int J Technol Assess Health Care. 2023;39(1):e40.

[14] Djulbegovic BH, I.; Greenland, S. Uncertainty in Clinical Medicine. In: Gifford FVE, Dov M. Gabbay, Paul Thagard and John Woods. General Editors., ed. Handbook of the Philosophy of Science. Volume 16: Philosophy of Medicine. Vol 16. Elsevier 2011:300-356.

[15] Eichler HG, Bloechl-Daum B, Brasseur D, et al. The risks of risk aversion in drug regulation. Nat Rev Drug Discov. 2013;12(12):907-916.

[16] Djulbegovic B. Articulating and responding to uncertainties in clinical research. J Med Philos. 2007;32(2):79-98.

[17] Zimmermann H-J. An application-oriented view of modeling uncertainty. European Journal of Operational Research. 2000;122(190-8).

Data and evidence on the way to clinical research

Professor Christof von Kalle | BIH Chair for Clinical-Translational Sciences and Founding Director of the Joint Clinical Study Centre of BIH and Charité | Dr Mona Rams, Dr Stefanie Rudolph | Clinical Study Centre of the Berlin Institute of Health (BIH) at Charité

Evidence-based medicine combines scientific findings from various fields of research with the aim of improving people's health and quality of life. Clinical studies, especially randomised controlled trials (RCTs), are considered the gold standard for evaluating interventions and provide robust evidence for cause-and-effect relationships. However, RCTs are reaching their limits for practical and ethical reasons. The increasing availability of data and advances in the field of artificial intelligence (AI) open up new possibilities for medical research and patient care. Real-world data (RWD) provides insights into the long-term and real-life effects of therapies. In combination with AI-driven analyses and modern statistical methods, RWD have the potential to significantly complement RCTs. To ensure this, data and outcomes of every medical intervention should be processed and evaluated digitally in the future. This could substantially enhance the development of personalised therapies and the efficiency of healthcare.

Introduction: Navigating the complexity of healthcare with evidence-based medicine

Medical research has one overarching goal: to improve people's health and quality of life. To achieve this, disease mechanisms are explored, and potential interventions are developed and subsequently assessed for their effectiveness. A cornerstone of medical research is evidence-based medicine (EBM), which aims to make the best possible treatment decisions based on the latest scientific findings. This approach relies on a variety of research methods, from basic laboratory research to clinical studies on patients.

In basic science, the measured value from experiments has always been regarded as the highest form of evidence. Similarly, in evidence-based medicine, basic research forms the foundation for a deeper understanding of how potential therapies work at a molecular and cellular level. According to this concept, fundamental mechanisms of diseases and potential therapeutic targets are investigated experimentally in the laboratory. Basic medical research often includes in vitro studies, such as the investigation of receptor binding at the molecular level, cell culture analyses, and preclinical in vivo models.

While results from basic research represent a very clear form of evidence, they are rarely directly transferable to applications in living systems. Thus, the most promising findings are further investigated in preclinical and clinical research through correlative studies. Preclinical research, which precedes clinical trials, acts as a bridge between basic research and human application. It focuses on investigating the safety and efficacy of mechanisms, pharmaceuticals, or treatments, particularly concerning physiological or molecular endpoints. Strict controlled conditions are applied, primarily using laboratory or animal models. However, similar to basic research, the transfer of preclini-

cal findings to humans is also challenging because results from animal studies may not always be directly applicable to humans. The extrapolation of findings from preclinical studies to human populations requires careful consideration of physiological differences, genetic variations, and species-specific responses to therapies. Moreover, statistical analysis often relies on limited data from laboratory investigations, imaging studies, and molecular assays, making assumptions about normal distribution, homogeneity of variance, and independence and randomisation.

Following basic and preclinical research, clinical research assesses the safety, efficacy, and effectiveness of treatments, pharmaceuticals, diagnostic tools, and interventions directly in human populations. The focus is on patient-centred outcomes such as survival and quality of life. Challenges include ethical considerations related to patient recruitment, variability within human populations, and various confounding factors such as comorbidities and lifestyle, all of which can influence the outcomes. Data collection involves a wide range of variables, including standardised assessment procedures, medical records, and patient-reported outcomes. This variety of measurement points as well as missing data, data outliers and the presence of confounding variables and biases are common challenges that complicate data analysis and often require complex statistical assumptions.

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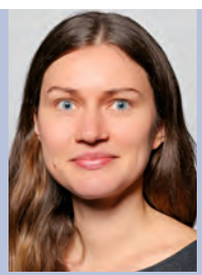


Dr Stefanie Rudolph *is a biologist and has been working as a scientific consultant at the Clinical Study Centre of the Berlin Institute of Health (BIH) at Charité since 2019, with a particular focus on digitalization processes in oncology. Prior to this, she was employed at the NCT Heidelberg.*

Dr Mona Rams *studied bioinformatics and completed her doctorate in this field, specialising in machine learning and algorithm development for precision oncology. Since 2023, she has been serving as a scientific advisor at the Clinical Study Centre of the Berlin Institute of Health (BIH) at Charité.*

Comparison of the characteristics of RCTs and RWD studies

Characteristic	RCTs	RWD studies
Objective	Collect evidence for efficacy and safety	Long-term effects, everyday use, rare events
Design	Prospective, randomised controlled study	Generally retrospective observational study
Data source	Data collection during the study	Routine health data, registry data
Sample size	Relatively small, controlled selection of participants	Potential very large, representative samples from the real world
Areas of application	Testing the efficacy and safety of new therapies	Generation of hypotheses, identification of risk factors, evaluation of long-term effects
Costs	High costs due to recruitment, intervention and data collection	Relatively lower costs as data from existing sources is used
Time required	Long time until results are found	Faster time frame to results
Existence of	Yes	Not applicable in some cases
Strengths control groups	High internal validity, strong causality statements possible	High external validity, representative results for the real world
Weaknesses	Limited generalisability, high costs, time-consuming	Higher risk of selection bias, few opportunities for intervention

Source: Own presentation

Figure 1: Comparison of various features of randomised controlled trials (RCTs) and real-world data (RWD) studies.

The gold standard: randomised controlled trials in clinical research and their limitations

Randomised controlled trials (RCTs) are considered the gold standard in clinical research because they provide the strongest evidence for the efficacy and safety of interventions. Their design specifically aims to minimise the influence of the aforementioned confounding factors through randomisation, thereby establishing a clear cause-and-effect relationship between the intervention and observed outcomes.

Randomisation is a fundamental component of RCTs, whereby participants are randomly assigned to either the intervention group or the control group. The intervention group receives the treatment being investigated, while the control group receives a placebo, standard treatment, or no intervention. Randomisation helps control for potential confounding factors such as underlying health conditions or lifestyle habits that could affect the outcomes. By masking treatment allocation to participants and researchers, blinding reduces detection and performance bias as much as possible.

RCTs offer significant advantages. They allow precise measurement of treatment efficacy and short-term toxicity in a highly controlled environment. This allows for clear

comparisons between the intervention and control groups, providing strong evidence for cause-effect relationships in healthcare.

Nevertheless, RCTs are not fully applicable to all situations. Ethical considerations may arise that militate against conducting RCTs, especially if withholding proven beneficial treatments from the control group. Additionally, recruiting enough participants, ensuring proper blinding, and the high costs of RCTs present significant practical challenges.

Moreover, the controlled environment of RCTs can limit the generalisability of the results to real-world clinical practice. The wide variability of patient populations, e.g. in terms of ethnic diversity or health status, cannot usually be fully mapped. Strict adherence to treatment protocols can also restrict the transferability and applicability of findings to the real world. Lastly, studying rare diseases with RCTs can be difficult due to the limited number of available patients, making it challenging or even impossible to obtain statistically significant data in such cases (Wicherski et al., 2023).

Real-world data (RWD)

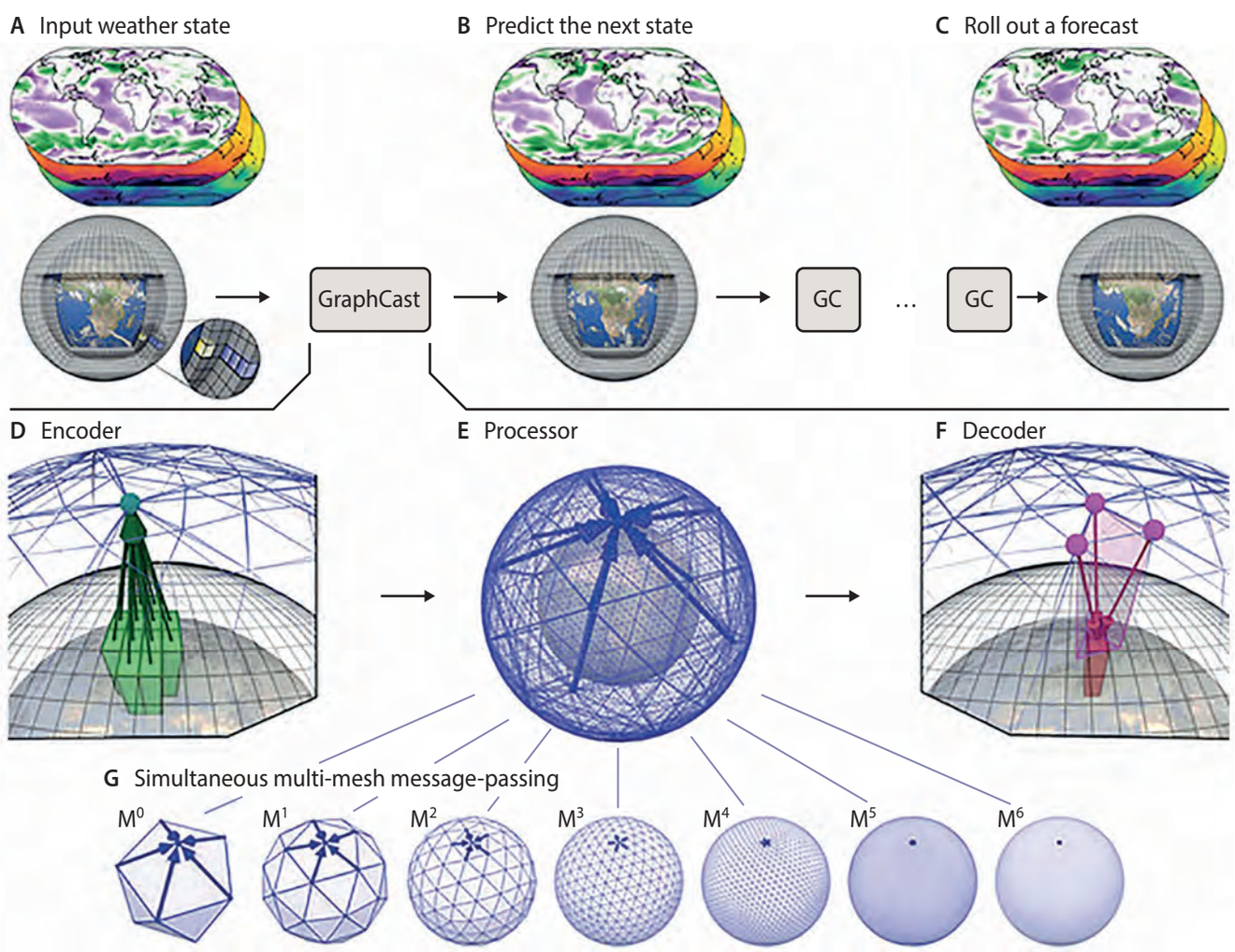
Given the limitations of RCTs mentioned above, there is an urgent need for alternative approaches to generating statistically significant results in the clinical context. One approach is the analysis of real-world data (RWD). RWD comprises everyday health data that is not collected for research purposes but is routinely generated in the course of patient care or may originate from other sources. This includes electronic health records, billing data, registry data, or information from wearable devices connected to health apps. These data reflect the true diversity of the patient population, including factors such as age, gender, comorbidities, and the actual use of pharmaceuticals in practice.

Analysing RWD offers several advantages over RCTs (figure 1). Firstly, RWD studies can provide insights into long-term effects, which are often not feasible in RCTs due to cost constraints. Additionally, RWD are collected under real-life conditions, making the results potentially more applicable to practical patient care. An added benefit is the possibility of identifying rare side effects that may be hidden in RCTs due to the controlled environment and limited participant numbers. In addition, RWDs offer an opportunity to obtain a sufficiently large amount of data, particularly in the case of rare diseases.

Despite the extensive possibilities RWD offers, gathering large amounts of data with the required level of detail to answer a specific research question is a major challenge. Especially obtaining detailed information, such as comprehensive capture of participant characteristics and a clear link between observed outcomes and the therapy studied, is often challenging outside the controlled environment of RCTs. At present, a further disadvantage of RWD is often the data quality, which can be highly variable or systematically flawed due to different collection practices in various institutions and the different purposes for which the data were initially collected (e.g., billing data). Data may also be missing or inconsistent.

Even though the challenges in evaluating RWD must be taken into account, the enormous potential of RWD studies for clinical research is significant. With increasing availability and improved data quality of RWD, along with the development of new statistical analysis methods, RWD analyses are becoming an increasingly important tool in the pursuit of a truly comprehensive assessment of the effectiveness and safety of therapies (Wicherski et al., 2023).

AI and complex correlations: Successes in weather forecasting and opportunities for medicine



Source: Lam et al., 2023

Figure 2: Methods based on artificial intelligence are applied in numerous fields. The figure shows an example of the use of artificial intelligence using the GraphCast method (Lam et al., 2023). GraphCast uses pattern recognition in complex weather data to generate precise forecasts. In 90 per cent of cases, GraphCast outperformed the accuracy of conventional weather models on supercomputer networks. The success of GraphCast demonstrates potential of AI for analysing complex systems to identify non-random correlations and patterns. It is likely that similar technologies in the future could complement or even replace existing statistical analysis methods in a similar way in medicine in the future helping to identify diseases more quickly and analyse the effectiveness of individual treatment strategies in complex data environments.

Using real-world data for health technology assessment

According to current understanding, RCTs remain the preferred method for the evaluation and approval of new health technologies. However, there are already several examples where RWD analyses have been used. For the approval of the COVID-19 vaccines Comirnaty® and Vaxzevria®, existing RCTs did not provide clear evidence of efficacy in individuals over 60 years of age. Therefore, RWD were evaluated for a comprehensive assessment. The RWD came from electronic health records in Scotland, which include data on GP care, laboratory tests, hospitalisations, and the death registry. Combined with data from vaccination registries, a prospective cohort study could be conducted in real-time. Another example is Blinatumomab, an anti-cancer pharmaceutical. Here, a historical control group based on pooled RWD supplemented the single-arm clinical trial. These additional data significantly contributed to speeding up the approval process (Wicherski and Haenisch, 2024).

The above examples illustrate that the evaluation of RWD can provide a more nuanced understanding of the effectiveness and safety of health technologies, enabling more informed decisions for patient care. To fully realise the potential of RWD, data quality must continue to improve, relevant RWD sources must be made more accessible, methods for evaluating RWD must be further developed, and the importance of RWD in regulatory practice must be more firmly established.

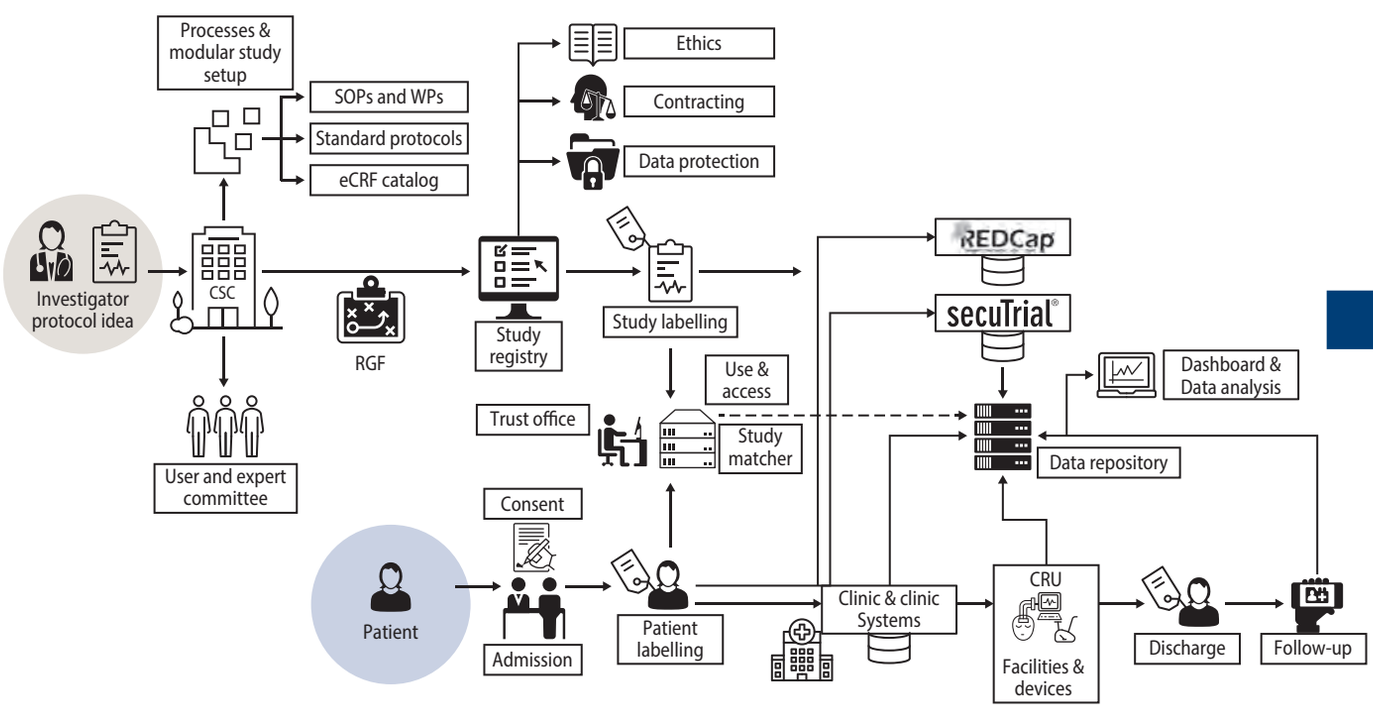
Artificial intelligence: expecting the unexpected

Artificial intelligence (AI) comes into play with the potential availability of very large amounts of data, particularly from RWD. According to Bitkom and the German Research Centre for Artificial Intelligence, AI refers to the „ability of an IT system to display ‚human' intelligent behaviour" (Weber & Buschbacher 2017). Generative AI is a particularly exciting development within AI. Based on training data, which can include images, text, or code, it can generate entirely new data in complex analogies. For example, it can create images that are modelled on a specific style or compose new pieces of music. Another important direction in AI is large language models (LLMs). These are based on natural language processing, enabling communication with machines in human language and thinking. LLMs have significantly simplified access to AI methods for many people and the scientific community.

Thanks to LLMs, scientists and developers can now use and integrate powerful AI tools into their work without relying on expensive supercomputers. One example comes from meteorology: today, AI systems in laptop format can produce lightning-fast weather forecasts that rival those of meteorological services (Voosen 2023, figure 2). Another example comes from chemistry: an AI chatbot demonstrated strong performance in predicting chemical properties and reactions (Jablonka et al., 2024). Even the deciphering of historical documents benefits from AI, which for the first time decoded passages from a rolled-up papyrus scroll from Herculaneum (Marchant, 2024).

These examples show that multidisciplinarity is not a challenge for AI. It has also already found its way into clinical research. AI can make a valuable contribution to the benefit of patients at all levels of clinical studies, but also in the prevention and treatment of patients in general. It has been shown that AI can perform screening for patient inclusion in oncology studies comparably to, if not better than, manual screening. At the same time, AI is highly efficient due to the time saved and reduced personnel costs (Chow et al., 2023). Similar to the earlier example of predicting chemical properties, AI can also be used to improve

Data streams in the digital health ecosystem: from fragmentation to interconnectedness



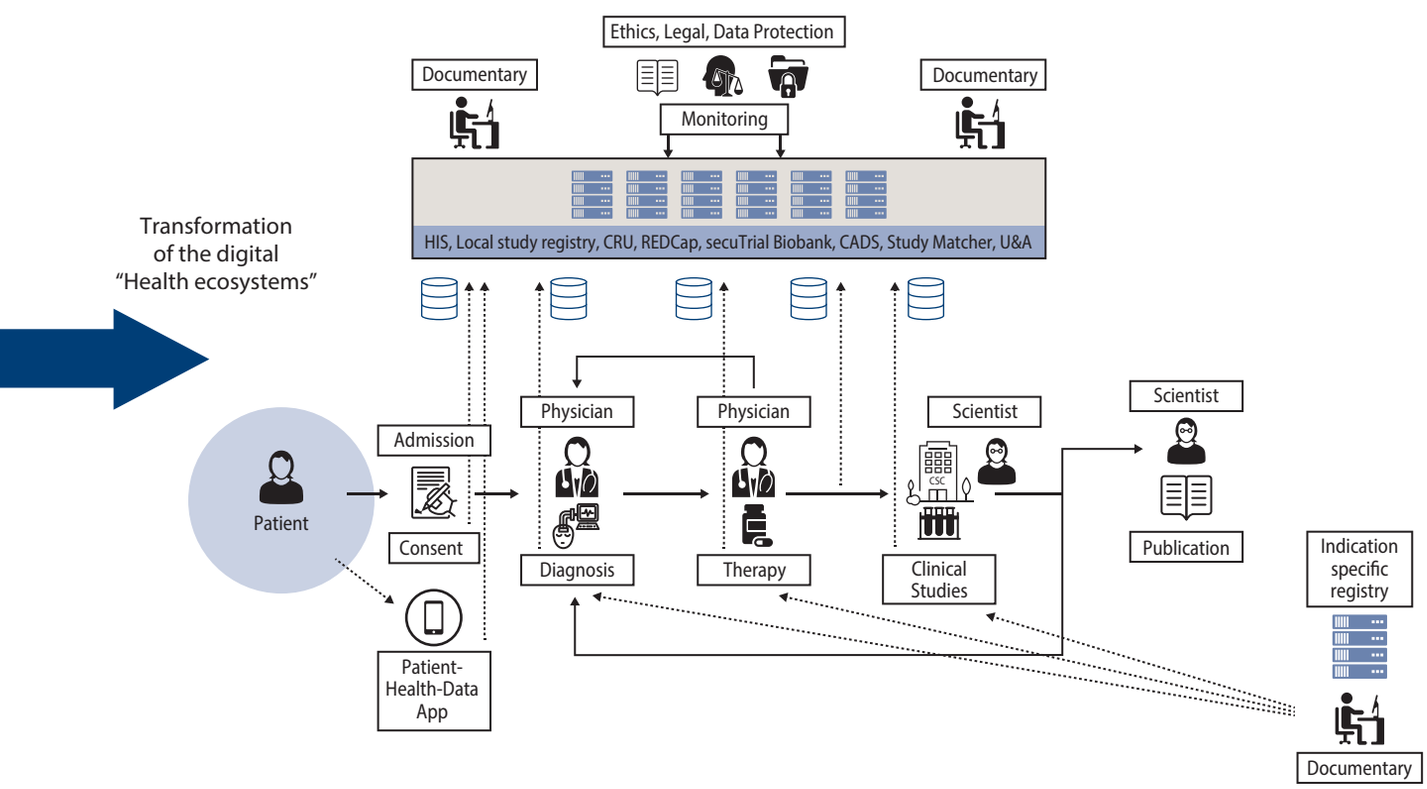
Quelle: own presentation © Symbols: Flaticons.com

Figure 3: The left-hand side of the figure shows the existing, historically developed data environment of a university hospital's digital health ecosystem. It consists of many individual data processes, a large proportion of which still includes analogue components and interact partially or not at all in a complex network.

antibodies for therapeutic purposes (Callaway, 2023).

Another field of application for AI could be screening. After training a ChatGPT-like base model, scientists were able to detect eye diseases using unmarked retinal images. This model can be adapted for various applications, such as evaluating Parkinson's risk (Zhou et al., 2023). Further examples of future AI use in clinical trials include pharmacovigilance (Edrees et al., 2022) and data curation and utilisation for clinical research (Wu et al., 2024). To further enhance trust in AI-supported systems, there are now approaches that allow AI to explain its decisions transparently, such as the reasoning behind the diagnosis of melanoma (Chanda et al., 2024).

AI can also support research institutions and clinical



The right-hand side of the figure shows the ideal structure as a future strategy for such a system. Data streams from care, studies, and everyday health data are captured interoperably in a patient-centred data backbone and made available for treatment, research, and quality assurance according to the patient's wishes and requirements.

study centres in many ways. The Clinical Study Centre at the Berlin Institute of Health at Charité (BIH) is working on AI applications to support the development of standardised study protocols, improve data quality, and provide patients with more comprehensive information as part of an extended consent process (Broad Consent), thereby involving them more deeply in their treatment decisions.

Data quality and data utilisation

High-quality data and its effective utilisation are key to successful medical research. To achieve these goals, close collaboration between researchers, patients, and their re-

presentatives is essential. The basis for this is patient-centred clinical research, where the patient is at the centre, to find the best possible treatment for each individual patient with the involvement of those affected. Patient organisations and advocacy groups can actively participate in the design of clinical studies. The aim of patient-oriented clinical research continues to be the development of prevention strategies, the improvement of treatment with a high quality of life for patients, the optimisation of structures in the healthcare system and the creation of information and study results that are understandable for patients.

The analysis of RWD, i.e. the analysis of large and complex data sets, is indispensable for achieving the objectives of patient-oriented research described above and offers a wide range of possibilities. Access to such data is still hindered for various reasons. One reason is, for example, that our digital health ecosystem is currently a complex system composed of many isolated data processing and storage processes (see figure 3 on the left). Clinical trials are an exception, as data is usually collected centrally.

With the various new digital laws, such as the Health Data Utilisation Act, data exchange should be advanced in the future. A systematic data exchange lays the foundation to enable or promote current innovations in medicine and data analysis methods and thus actually generating added value for patients. The aim must be to create an interoperable environment in which data from different projects can be easily exchanged and analysed together, even across sectors (see Figure 3 on the right).

The current developments in all involved areas hold great potential. For each patient, a customised clinical study could be conducted in the future. It should be noted that a significant proportion of patients with rare diseases are in routine care without their disease being diagnosed. By intelligently linking data from various sources, such diseases could be detected more quickly in the future, and targeted therapies could be developed.

From research to patients and back: the power of translation

Translation – the transfer of findings from basic research to clinical application and vice versa – is needed to quickly bring the progress made in research to patients. To further advance translation for the benefit of patients, a change in thinking is required. In oncology, we need a Vision Zero.

Vision Zero is a concept originally from road safety research. The aim of Vision Zero is to prevent all avoidable fatalities in the respective area. Previous strategies in accident research often focussed on reducing the total number of collisions. Human error was identified as the main cause of accidents This resulted in costly measures to improve human behaviour on an imperfect road system. A new approach to translation enabled a change in thinking and brought forth new insights. Instead of only minimising the number of accidents, the focus was now on preventing fatalities and serious injuries. Defects in the traffic system itself were identified as the cause of accidents and the focus was on using perfect road systems to compensate for imperfect human behaviour.

Vision Zero in oncology means preventing the development of cancer wherever possible and significantly improving the chances of cure for all cancers, or at least enabling patients with cancer to enjoy a consistently high quality of life in the future. The underlying concepts include prevention measures, early detection, improved treatment methods, and comprehensive care. The aim is therefore to exploit the full range of possibilities, leaving no stone unturned, to save lives and minimise suffering caused by cancer.

One example of successful translational research in

oncology is the implementation of national programmes for genomic medicine. The German Consortium for Hereditary Breast and Ovarian Cancer (DKH-funded) and the National Network for Genomic Medicine (nNGM) Lung Cancer (DKH-funded) are researching genetic correlations in cancer and now include nearly two-thirds of affected patients in Germany. The example of the nNGM programme shows that involved patients in care demonstrably benefit from a significantly higher survival rate (Kästner et al., 2024).

Conclusion: Medicine of the future – data, AI, and new standards

Although molecular and mechanistic research often provides the highest level of evidence in science, evidence-based medicine focussed purely on correlation sometimes reaches its limits. Artificial intelligence (AI) is expected to significantly improve the availability and quality of clinical and other real-world data. AI-supported analyses and modern statistical methods have the potential to supplement, or even replace, randomised clinical studies based on this data, provided the observational data is of high quality and the design is prospective.

Therefore, the data and results of every medical intervention should be digitally processed and analysed in the future, just as it is taken for granted in other areas of life for safety-relevant or even life-critical technologies and measures. The enormous potential of a comprehensive data basis can then be used to develop even more targeted and effective treatment and diagnostic procedures and to further decisively improve medical care for the benefit of patients.

References

[1] Callaway E. 2023. How generative AI is building better antibodies. Nature 617:235.

[2]Chanda T, Hauser K, Hobelsberger S, Bucher T-C, Garcia CN, Wies C, Kittler H, Tschandl P, Navarrete-Dechent C, Podlipnik S, Chousakos E, Crnaric I, Majstorovic J, Alhajwan L, Foreman T, Peternel S, Sarap S, Özdemir İ, Barnhill RL, Llamas-Velasco M, Poch G, Korsing S, Sondermann W, Gellrich FF, Heppt MV, Erdmann M, Haferkamp S, Drexler K, Goebeler M, Schilling B, Utikal JS, Ghoreschi K, Fröhling S, Krieghoff-Henning E, Salava A, Thiem A, Dimitrios A, Ammar AM, Vučemilović AS, Yoshimura AM, Ilieva A, Gesierich A, Reimer-Taschenbrecker A, Kolios AGA, Kalva A, Ferhatosmanoğlu A, Beyens A, Pföhler C, Erdil DI, Jovanovic D, Racz E, Bechara FG, Vaccaro F, Dimitriou F, Rasulova G, Cenk H, Yanatma I, Kolm I, Hoorens I, Sheshova IP, Jocic I, Knuever J, Fleißner J, Thamm JR, Dahlberg J, Lluch-Galcerá JJ, Figueroa JSA, Holzgruber J, Welzel J, Damevska K, Mayer KE, Maul LV, Garzona-Navas L, Bley LI, Schmitt L, Reipen L, Shafik L, Petrovska L, Golle L, Jopen L, Gogilidze M, Burg MR, Morales-Sánchez MA, Sławińska M, Mengoni M, Dragolov M, Iglesias-Pena N, Booken N, Enechukwu NA, Persa O-D, Oninla OA, Theofilogiannakou P, Kage P, Neto RRO, Peralta R, Afiouni R, Schuh S, Schnabl-Scheu S, Vural S, Hudson S, Saa SR, Hartmann S, Damevska S, Finck S, Braun SA, Hartmann T, Welponer T, Sotirovski T, Bondare-Ansberga V, Ahlgrimm-Siess V, Frings VG, Simeonovski V, Zafirovik Z, Maul J-T, Lehr S, Wobser M, Debus D, Riad H, Pereira MP, Lengyel Z, Balcere A, Tsakiri A, Braun RP, Brinker TJ, Reader Study C. 2024. Dermatologist-like explainable AI enhances trust and confidence in diagnosing melanoma. Nature Communications 15:524. doi: 10.1038/s41467-023-43095-4. https://doi.org/10.1038/s41467-023-43095-4

[3] Chow R, Midroni J, Kaur J, Boldt G, Liu G, Eng L, Liu F-F, Haibe-Kains B, Lock M, Raman S. 2023. Use of artificial intelligence for cancer clinical trial enrollment: a systematic review and meta-analysis. JNCI: Journal of the National Cancer Institute 115:365-374. doi: 10.1093/jnci/djad013. https://doi.org/10.1093/jnci/djad013

[4] Edrees H, Song W, Syrowatka A, Simona A, Amato MG, Bates DW. 2022. Intelligent Telehealth in Pharmacovigilance: A Future Perspective. Drug Safety 45:449-458. doi: 10.1007/s40264-022-01172-5. https://doi.org/10.1007/s40264-022-01172-5

[5] Jablonka KM, Schwaller P, Ortega-Guerrero A, Smit B. 2024. Leveraging large language models for predictive chemistry. Nature Machine Intelligence 6:161-169. doi: 10.1038/s42256-023-00788-1. https://doi.org/10.1038/s42256-023-00788-1

[6] Kästner A, Kron A, van den Berg N, Moon K, Scheffler M, Schillinger G, Pelusi N, Hartmann N, Rieke DT, Stephan-Falkenau S. 2024. Evaluation of the effectiveness of a nationwide precision medicine program for patients with advanced non-small cell lung cancer in Germany: a historical cohort analysis. The Lancet Regional Health–Europe 36. doi: 10.1016/j.lanepe.2023.100788

[7] Marchant J. 2024. First passages of rolled-up Herculaneum scroll revealed. Nature 626:461-462.

[8] Lam R, Sanchez-Gonzalez A, Willson M, Wirnsberger P, Fortunato M, Alet F, Ravuri S, Ewalds T, Eaton-Rosen Z, Hu W, Merose A, Hoyer S, Holland G, Vinyals O, Stott J, Pritzel A, Mohamed S, Battaglia P. 2023. ‚Learning skillful medium-range global weather forecasting', Science, 382: 1416-21. https://doi.org/10.1126/science.adi2336

[9] Voosen P. 2023. AI is set to revolutionize weather forecasts. Science (New York, NY) 382:748-749.

[10] Weber M, Buschbacher F. 2017. ‚Künstliche Intelligenz–Wirtschaftliche Bedeutung, gesellschaftliche Herausforderungen, menschliche Verantwortung', Bitkom e. V., DFKI, Berlin, Kaiserslautern.

[11] Wicherski J, Haenisch B. 2024. Die Anwendung von Real-world-Evidenz in Entscheidungsprozessen der Arzneimittelregulation. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz 67:149-154. doi: 10.1007/s00103-023-03830-0. https://doi.org/10.1007/s00103-023-03830-0

[12] Wicherski J, Schneider K, Zinserling J, Heß S, Haenisch B, Broich K. 2023. Real-world-Daten in der Arzneimittelregulation – aktuelle Entwicklungen und Ausblick', Prävention und Gesundheitsförderung. https://doi.org/10.1007/s11553-022-01010-7

[13] Wu X, Li W, Tu H. 2024. Big data and artificial intelligence in cancer research. Trends in Cancer 10:147-160. https://doi.org/10.1016/j.trecan.2023.10.006

[14] Zhou Y, Chia MA, Wagner SK, Ayhan MS, Williamson DJ, Struyven RR, Liu T, Xu M, Lozano MG, Woodward-Court P, Kihara Y, Allen N, Gallacher JEJ, Littlejohns T, Aslam T, Bishop P, Black G, Sergouniotis P, Atan D, Dick AD, Williams C, Barman S, Barrett JH, Mackie S, Braithwaite T, Carare RO, Ennis S, Gibson J, Lotery AJ, Self J, Chakravarthy U, Hogg RE, Paterson E, Woodside J, Peto T, McKay G, McGuinness B, Foster PJ, Balaskas K, Khawaja AP, Pontikos N, Rahi JS, Lascaratos G, Patel PJ, Chan M, Chua SYL, Day A, Desai P, Egan C, Fruttiger M, Garway-Heath DF, Hardcastle A, Khaw SPT, Moore T, Sivaprasad S, Strouthidis N, Thomas D, Tufail A, Viswanathan AC, Dhillon B, Macgillivray T, Sudlow C, Vitart V, Doney A, Trucco E, Guggeinheim JA, Morgan JE, Hammond CJ, Williams K, Hysi P, Harding SP, Zheng Y, Luben R, Luthert P, Sun Z, McKibbin M, O'Sullivan E, Oram R, Weedon M, Owen CG, Rudnicka AR, Sattar N, Steel D, Stratton I, Tapp R, Yates MM, Petzold A, Madhusudhan S, Altmann A, Lee AY, Topol EJ, Denniston AK, Alexander DC, Keane PA, Eye UKB, Vision C. 2023. A foundation model for generalizable disease detection from retinal images. Nature 622:156-163. doi: 10.1038/s41586-023-06555-x. https://doi.org/10.1038/s41586-023-06555-x

Discussion points with the speakers: Chronic diseases and HTA procedures in Austria

Professor Jürgen Wasem | Chair of Medical Management at the Faculty of Economics and the Faculty of Medicine at the University of Duisburg-Essen

Adaptation of study designs for chronic diseases to avoid data gaps:
In the G-BA's benefit assessment procedures for new diabetes pharmaceuticals, a larger number of subgroups with different comparators are regularly defined based on previous therapies. Manufacturers note that this leads to significant data gaps from the outset, often resulting in a conclusion of „no additional benefit".

However, unlike targeted therapies in the orphan drug area, the number of diabetes patients is large, and the subgroups and their G-BA comparators are essentially known. Therefore, it raises the question of what efforts are being made by manufacturers to adapt study designs to meet G-BA requirements. The design of studies with multiple study arms, including corresponding subgroups and associated comparators, should be considered in the design of approval programs.

Consideration of changing treatment standards:
Studies on chronic diseases sometimes require very long periods before patient-relevant endpoints show statistically significant differences between the intervention and control arms. Consequently, the medication used in the control arm may no longer represent the current standard of care by the end of the study, posing a considerable risk that the G-BA will not recognise any additional benefit.

To address this challenge, the G-BA could be required to consider the comparator used in the study for benefit assessment if it was adequate at the time the study was planned. Despite the evident difficulties in collecting comparative study data in such situations, it should be part of the innovative industry's self-image to measure itself against the best competing therapeutic standards.

Could an alternative approach of dealing with this dilemma be for the G-BA to conduct an added benefit assessment compared to the current standard of care, but also to determine that the (now outdated) study comparator was adequate at the start of the study? This could then be considered in the context of price negotiations, among other things.

Optimisation of regulation and flexibility in the HTA procedure:
During the introduction of the AMNOG procedure in Germany, the term „learning system" was frequently used. Both elements belong together in a functioning system: clear specifications and framework conditions on one hand and

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flexibility and adaptability on the other. Regarding European partner countries, the question arises about the established discussion and decision-making structures there.
Where do legal requirements apply, and what is regulated more „informally"? How much regulation – and thus a certain rigidity – and how much unregulated freedom is needed for HTA?

Chronic diseases in AMNOG – how do we create reliable framework conditions for innovation?

Tobias Gemmel and Dr Eberhard Lüdtke | Novo Nordisk Pharma GmbH*

Based on an empirical analysis of 849 AMNOG procedures from 2011 to 2023, it has been demonstrated that especially chronic diseases are disadvantaged by the AMNOG methodology. This was shown, among other things, by the fact that – compared to oncology products – the „considerable" and „significant" additional benefit categories were achieved significantly less frequently, with one driving factor being the lack of differences in mortality. This disadvantage is further reinforced by the AMNOG guidelines set out in the GKV Financial Stabilisation Act (GKV-FinStG), as the „minor" and „non-quantifiable" categories have been downgraded and were hardly achieved in the past in the case of chronic diseases. The challenge in chronic diseases also lies in the fact that patient-relevant endpoints of late and secondary complications, according to the AMNOG methodology, lie far in the future and other care-relevant endpoints are not recognised (surrogate endpoints). Against this background, we believe it is essential to withdraw the AMNOG guidelines from the GKV-FinStG. For us, a fundamental structural reform of the AMNOG is mandatory to solve the disadvantages of the benefit assessment procedure, especially for chronically ill patients. In addition to ensuring the reliability of G-BA consultations, particularly when determining the appropriate comparator therapy (ACT), we also call for the acceptance of therapy goals defined in guidelines and Disease Management Programmes (DMPs) as patient-relevant endpoints.

**Based on two internal projects by Novo Nordisk Pharma GmbH, with the support of J. Hotzy, K. Knerr-Rupp, D. Kuckelsberg, V. Stückemann (all Novo Nordisk), H. Bleß (fbeta GmbH), and T. Volmer (SmartStep Consulting GmbH).*

Introduction

The benefit assessment process was designed as a learning system to adapt to ever-changing conditions. Based on this claim, a meaningful amendment of the benefit assessment must take greater account of the needs of people with chronic diseases. However, when the GKV-FinStG came into force in 2023, the primary focus was on addressing the cost situation of statutory health insurance, and the parameters for price determination in the benefit assessment process were changed, which further significantly burdened pharmaceuticals for the treatment of chronic diseases.

Instead, a return to the original idea introduced with the German Pharmaceutical Market Reorganisation Act (AMNOG) would be desirable, namely, to negotiate a benefit-adjusted price based on high-quality evidence of benefit. Reliable framework conditions are a prerequisite for developing incremental innovations, which are particularly important for the care of chronically ill patients.

Specifics of chronic diseases in the AMNOG procedure

Since the introduction of AMNOG in 2011, the aim of early benefit assessment has been to ensure optimised care with innovative pharmaceuticals based on the assessment of evidence from the patient's perspective. One of the core rules so far has been that the reimbursement of a pharmaceutical without proven additional benefit must not lead to higher expenditures than the cheapest available comparator therapy. This ensured that any additional expenditure was always accompanied by a proven gain in patient-relevant benefit and that pharmaceutical costs could be justifiably linked to the additional benefit.

In this way, a fundamentally functioning system of benefit assessment and price negotiation has emerged, which in the vast majority of cases leads to a balance of interests

between the National Association of Statutory Health Insurance Funds (GKV-SV) and the pharmaceutical companies, and thus to a mutually agreed negotiation result on the reimbursement amount.

High-priced pharmaceuticals are primarily biologics, oncology products, and pharmaceuticals for the treatment of rare diseases (orphan drugs). Pharmaceuticals in indications where short-term effects can be achieved have a very good chance of obtaining an additional benefit.

This is particularly evident in oncology, where effects on overall survival can be demonstrated in advanced diseases with relatively short study durations.

Pharmaceuticals for the treatment of chronic diseases face significantly higher hurdles. On the one hand, this is due to the lack of recognition of patient-relevant endpoints (surrogates), such as those specified in guidelines and disease management programmes (DMPs). At the same time, pharmaceuticals for the treatment of chronic diseases aim to prevent late and secondary complications, which can only be demonstrated in long-term outcome studies. Such studies cannot de facto be available at the time of approval due to the long study duration of a pharmaceutical.

These specific hurdles were pointed out early on. In their joint position paper „Early benefit assessment of new pharmaceuticals 2019 – fair and sustainable?" the German Society for Haematology and Medical Oncology (DGHO) and the Association of the Scientific Medical Societies (AWMF) come to the following unanimous conclusion: „The current metho-

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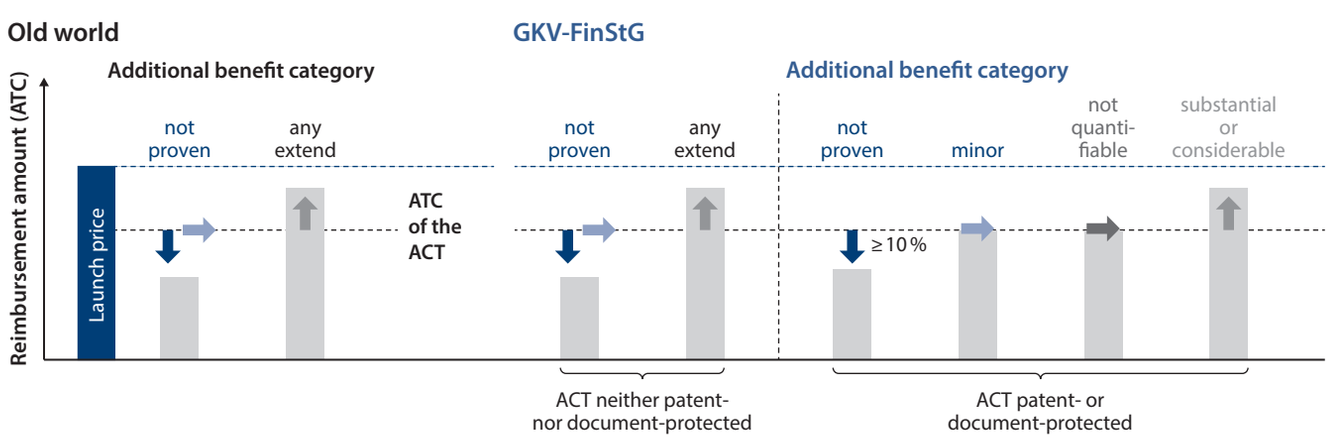
Dr Eberhard Lüdtke, *Director National Market Access. After studying pharmacy and gaining a doctorate, he joined the pharmaceutical industry in 1992 as Junior Product Manager at Desitin GmbH. In 1995, he joined Lundbeck GmbH in the Marketing department, becoming head of marketing in 1998. Since 2011, his focus has been on AMNOG and conducting benefit assessments, including price negotiations. In October 2017, he changed to IGES as a Senior Advisor for Market Access. Since April 2018, he has been the Director of National Market Access at Novo Nordisk Pharma GmbH, responsible for AMNOG processes.*

dology of early benefit assessment primarily favours disease indications with short life expectancy and pharmaceuticals with orphan drug status. Chronic diseases with a long course of therapy and disease are at a disadvantage. This imbalance will have a long-term negative impact on the development of new pharmaceuticals.[1]

The situation has been further exacerbated by the GKV-FinStG by significantly downgrading the benefit categories of pharmaceuticals with „minor" or „non-quantifiable" additional benefit. If the appropriate comparator therapy (ACT) is patent-protected, a mandatory price reduction of at least 10 per cent is prescribed if no additional benefit has been proven (figure 1). The benefit categories „minor" and „non-quantifiable" cannot negotiate a price surcharge on the ACT despite proven additional benefit.

This undermines the principle of appropriate remuneration, particularly for incremental innovations, based on the additional benefit, and limits incentives for the development and availability of new pharmaceuticals, especially for chronic diseases. This will have a long-term impact on the quality of care.

Presentation of the AMNOG guidelines according to GKVFinStG



The pressure on the manufacturer regarding an additional benefit has increased further!

GKV-FinStG: GKV Financial Stabilisation Act; ATC: Annual treatment costs; ACT: appropriate comparator therapy

Source Presentation by Ecker + Ecker on the occasion of the EUCOPE webinar "Drastic changes in Europe's 1st launch country: How recent legislative changes impact the German P&R landscape" of 15 March 2023 on the amendment of Section 130b (3) SGB V following the GKV Financial Stabilisation Act; available online at https://www.ecker-ecker.de/application/files/8116/7896/4728/E_plus_E_EUCOPE_Webinar_GKV-FinStG_and_BSG_final_2023-03-15.pdf (accessed on 20 June 2024)

Figure 1: If the G-BA determines one of the two additional benefit categories to be „minor" or „non-quantifiable", manufacturers can no longer negotiate a price premium on the ACT since the GKV-FinStG.

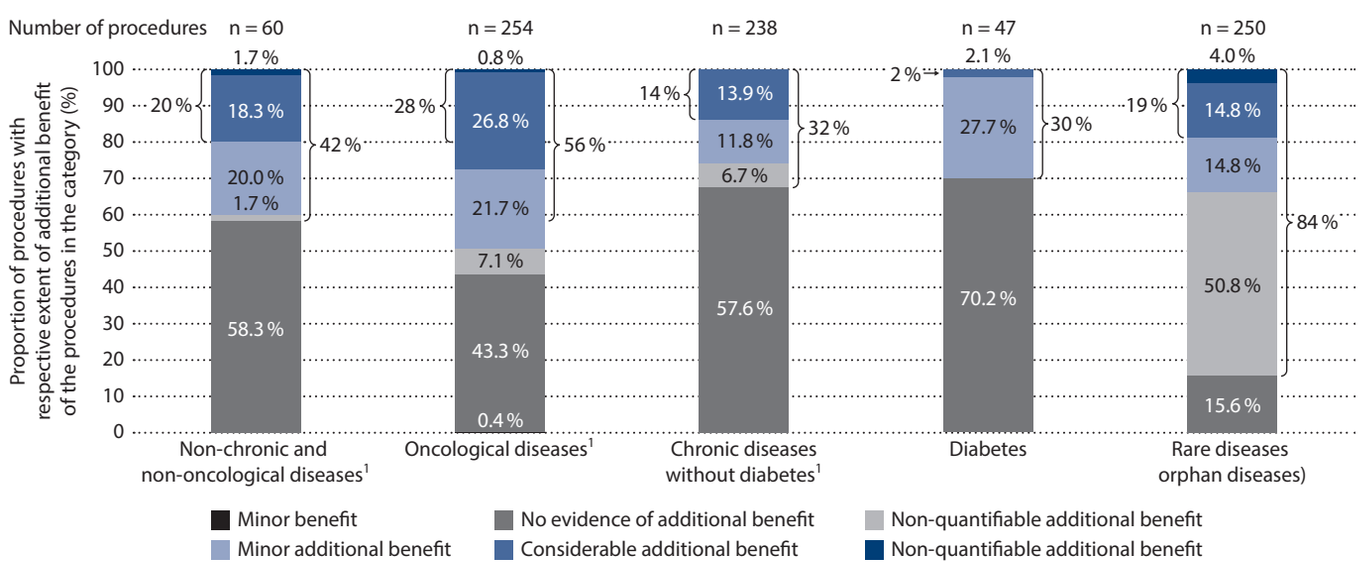
Empirical analysis confirms: pharmaceuticals for chronic diseases are at a disadvantage in the AMNOG

Excerpts from an empirical analysis focussing on pharmaceuticals for the treatment of chronic diseases within the scope of the AMNOG HTA assessments are presented below. All AMNOG procedures completed between the start of AMNOG on 1 January 2011 and 15 July 2023, 849 procedures were analysed regarding the benefit assessment. A definition of chronic diseases provided by the Joint Federal Committee (G-BA) was used.[2] Orphan drug procedures (n = 250) and procedures in oncological indications (n = 254) were classified into their specific categories separately and excluded from chronic diseases.

Overview of results for the additional benefit categories, mortality, and morbidity as well as study duration

Pharmaceuticals for the treatment of chronic diseases are generally more likely not to show an additional benefit in the German HTA assessment. Pharmaceuticals for diabetes

Proportion of additional benefit for chronic versus non-chronic diseases



1: Without rare diseases (orphan diseases)
A total of n = 849 completed AMNOG procedures, of which n = 285 procedures in connection with chronic diseases (15.07.2023), were taken into account in relation to completed procedures and the highest additional benefit realised. A product can have several procedures and subpopulations are not considered.

Source: Novo Nordisk's own presentation based on empirical analysis

Figure 2: Of the 47 benefit assessment procedures for diabetes mellitus products, only 30 per cent resulted in a determination of a benefit.

therapy have even lower chances of achieving a positive benefit assessment.

Of 254 procedures for oncological diseases, 56 per cent result in an additional benefit, of which 28 per cent have at least a considerable additional benefit. Of 238 procedures for chronic diseases (excluding the 47 procedures for diabetic diseases), 32 per cent result in an additional benefit, and 14 per cent have at least a considerable benefit. The considerable benefit category would allow a price premium above the costs of the comparator therapy (according to the GKV-FinStG). Only 30 per cent of the 47 diabetes mellitus procedures result in an additional benefit. Conversely, only a negligible two per cent of the procedures result in a considerable additional benefit, reflecting the lowest chance of negotiating an acceptable reimbursement amount under the new framework rules in the GKV-FinStG.

A challenge inherent in HTA and AMNOG for the evaluation of therapies arises from the relatively slow progression of chronic diseases themselves: Most chronic diseases and their symptoms develop continuously or in phases over a long period, sometimes over decades, before they lead to critical health conditions.[3] Most clinical studies in the field of chronic diseases can therefore only measure the impact on morbidity parameters, even if the study duration is long, as no significant mortality differences emerge due to the slow progression of the disease within the study duration.

Benefit recognition in morbidity and mortality for chronic versus oncological procedures

Oncological diseases

Benefit recognized in **Morbidity**

Benefit recognised in **Mortality**	Yes	No	Total
Yes	65	72	137
No	48	46	94
Total	113	118	231

- 46 = 185

Chronic diseases

Benefit recognized in **Morbidity**

Benefit recognised in **Mortality**	Yes	No	Total
Yes	3	0	3
No	64	4	68
Total	67	4	71

Procedures in oncologic diseases were examined, minus procedure with „ZsN not substantiated“ and „lower ZsN“.
Contains only procedures in which the G-BA also presented endpoint in the decision (n = 231), (13. September 2023).
Added benefit 231 – 46 = 185

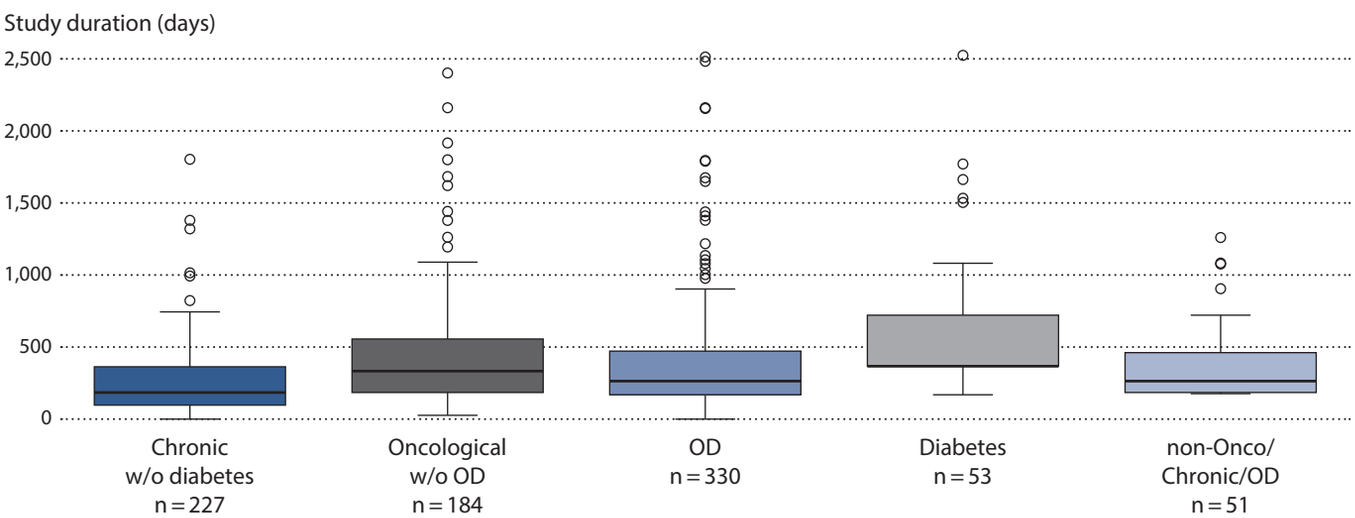
Source: Novo Nordisk's own presentation based on empirical analysis

Figure 3: In 39 per cent of procedures for oncology products, mortality benefits were the only driver for a positive benefit assessment, compared to 0 per cent of procedures for chronic diseases.

Chronic diseases thus show a significantly reduced benefit recognition within the mortality category. Mortality, on the other hand, is the main driver for positive benefit assessments for oncological procedures. In 74 per cent (137 out of 185) of the procedures with recognised additional benefit, mortality benefits contribute to a positive benefit assessment for oncological interventions. For chronic diseases, there were only three cases (four per cent) in which a mortality advantage was recognised (3 out of 67). For 39 per cent (72 out of 185) of oncological interventions, mortality benefits are the sole driver for a positive benefit assessment, compared to 0 per cent for interventions in chronic diseases (figure 3).

It is being discussed that pharmaceutical manufacturers only need to extend the duration of studies for chronic diseases in order to show corresponding results. Many companies have already taken this into account and have been conducting outcome studies for some time.

Evaluation of study duration



The study duration for diabetes is twice as long as for other chronic diseases and the longest in the AMNOG

845 studies are included - exclusion of studies that were not considered by the G-BA. Missing values in Dossier or G-BA/IQWiG resolution: observation duration imputed for missing study duration; for outcome-studies: treatment duration imputed as study duration for outcome studies; study duration is imputed for missing treatment duration.

Source: Novo Nordisk's own presentation based on empirical analysis

Figure 4: A comparison of the duration of studies for chronic diseases shows that the duration of studies for diabetes pharmaceuticals is twice as long as for other chronic diseases.

Comparing the study duration in chronic diseases with that of the other formed groups (figure 4) shows that the study duration for diabetes studies is already twice as long as for other chronic diseases and is the longest in the AMNOG processes. However, it often takes six to eight years to plan, conduct and analyse such outcome studies, i.e. they are generally not available at the time of approval. Even longer study periods cannot be realised and do not serve the principle of providing innovations to patients in a timely manner.

Three recommendations for further developing AMNOG from the perspective of chronic diseases

The analyses presented above suggest possible fields of action that should take into account the specific circumstances of treating chronic diseases within AMNOG. Three key points are presented below:

1. Abolition of AMNOG guidelines

In over ten years of the AMNOG, only around two per cent of pharmaceuticals for the treatment of chronic diseases have shown a considerable additional benefit, which is the basis for fair pricing in the AMNOG negotiations in accordance with the GKV-FinStG. In case of type 2 diabetes mellitus, for example, this is due in particular to the late complications and secondary complications that can only be measured much later in outcome studies and which, among other things, require long study durations.

Another provision in the GKV-FinStG stipulates that the lack of proof of superiority regarding patient-relevant endpoints leads to a price reduction of at least ten per cent if the ACT is patent-protected. With this regulation, new pharmaceuticals will in future be reimbursed at a lower rate than their patent-protected reference pharmaceuticals.

Beyond the breach with the previous fundamental principles of determining the reimbursement amount, the categorical design of the legal text („a reimbursement amount must be agreed") mainly prevents the negotiation partners from responding to particular care situations. Even in a situation where both parties are willing to reach an agreement, such an agreement would be legally prohibited. Against this background, the G-BA suggested in its statement that „exceptions to the mandatory requirements for reimbursement amount negotiations must be possible or that flexible „target regulations" be included in Section 130b SGB V".[4]

Professor Josef Hecken, impartial chairman of the G-BA, also recognises this problem. He recently wrote in an article in the AMNOG Report: „In the area of application of a chronic disease, it is likely that no long-term data is yet available for the market launch and that only the extent of a „minor" additional benefit can be inferred based on the study situation."[5] At an event, he added that the new guidelines „might be very harmful to the care of chronically ill patients." Hecken therefore called for: „In chronically ill patients for whom a positive endpoint is foreseeable as a result of the treatment, I would be in favour of deviating from the guidelines."[6] (The guidelines here refer to the framework regulations in the GKV-FinStG).

The AMNOG guidelines should be withdrawn so that chronic diseases are not disadvantaged in the benefit assessment process and that patients in Germany can continue to benefit from incremental innovations.

2. Binding nature of consultations

Early consultations are based on a legal right in accordance with Section 35a (7) SGB V, during which relevant aspects of the study design for new pharmaceuticals (PICOS) for benefit assessment are clarified at an early stage. Section 35a (7) SGB V also regulates the right of pharmaceutical companies

to obtain advice from the G-BA before submitting the dossier, particularly regarding the ACT and the documents and studies to be submitted for the benefit assessment.

The completeness of a dossier can only be ensured if the ACT and the subpopulations to be presented are known. An incomplete dossier, however, leads to non-recognition of additional benefit.

At the same time, consultation on the requirements for study design offers the opportunity to develop and conduct a relevant study for early benefit assessment at an early stage. For this reason, pharmaceutical companies routinely use this consultation before dossier submission or during study planning. The G-BA interprets the high utilisation of early consultations as „an indication that manufacturers want to improve their study design to generate reliable data for the subsequent benefit assessment."[7]

Notwithstanding this necessity and the legal right to consultation, Chapter 5, Section 7 (2) of the G-BA's procedural rules stipulates that the information provided by the G-BA during a consultation is not binding. The G-BA can amend the ACT in the ongoing procedure up to the time of the decision, thereby rendering a dossier created in reliance on the information provided worthless. In the decision, the non-recognition of an additional benefit is then justified by the fact that no data were provided by the pharmaceutical company in comparison to the ACT.

A possible change of the ACT, which may be necessary over time between consultation and decision-making due to new scientific findings, should regularly take the form of an expansion, but not replacing it. The fact that a newer therapy comprehensively replaces the previous therapy does not correspond to the reality of healthcare, even if there is an additional benefit. Particularly in light of the high demands for long study durations in chronic diseases, this would ensure that care-relevant significant evidence is considered in the benefit assessment and subsequent price negotiation.

3. Consideration of everyday care, DMPs, and guidelines in patient-relevant endpoints

In the treatment of chronic diseases, various aspects play a role, for example, when treating acutely life-threatening diseases. In the latter, the therapeutic goal is to prolong life expectancy while maintaining or improving quality of life. Therapeutically controllable chronic diseases, on the other hand, are generally not accompanied by restrictions in quality of life that can be objectively measured using AMNOG methods.

Therefore, treatment of chronic diseases often does not aim to have a direct effect on patients. Rather, the aim is to achieve guideline-compliant target values to avoid future negative events, such as a myocardial infarction, and to adhere to the respective therapy goals long-term while avoiding undesirable therapy effects as far as possible.

Guideline-based treatment of chronic diseases is often based on these target values, referred to as surrogates in the benefit assessment. However, these therapy parameters, relevant for approval, guidelines, and DMPs, are considered irrelevant to patients in the benefit assessment and are therefore completely ignored.

Based on the evidence currently available, the current National Disease Management Guideline (NVL) for diabetes recommends primarily reducing diabetes-related complications through the control of HbA1c as a surrogate for metabolic control.[8] The DMP Diabetes, committed to evidence-based medicine, also recommends HbA1c target values, whose adherence is monitored in the quality assurance of the DMPs. In its evaluation report on the DMP Diabetes, the Techniker Krankenkasse (TK) writes: „It is now considered established that good blood glucose control

significantly reduces the risk of diabetes-related microangiopathic late damage (retinopathy, nephropathy, neuropathy) and its progression."[9]

A similar practical treatment focus on surrogate parameters is also used for many other chronic diseases, such as hypertension, kidney disease, and neurological disorders.

To address the structural problems faced by pharmaceuticals for the treatment of chronic diseases in the benefit assessment and to enable an adequate and fair assessment of their benefit, the determination of patient-relevant endpoints should not conflict with defined treatment goals. Instead, the benefit of these pharmaceuticals should be measured by how well they fulfil their therapeutic purpose and achieve treatment-guiding or guideline-based endpoints (e.g. reaching HbA1c target ranges while avoiding hypoglycaemia, reducing weight, achieving target ranges for blood pressure, blood lipid levels, etc.).

Conclusion

- Withdrawal of the AMNOG guidelines of the GKV-FinStG, as incremental innovations that form the basis and rule for therapeutic progress in chronic diseases are devalued.
- Reliability in the development of therapies for chronic diseases through additional representation of the ACT defined in the G-BA consultation if this is no longer part of the ACT due to new scientific findings.

References

[1] German Society for Haematology and Medical Oncology, Position paper: Early benefit assessment of new pharmaceuticals 2019: Fair and sustainable? 2019.

[2] Federal Joint Committee, Decision of the Federal Joint Committee on an amendment to the Drug Guideline (AM-RL): Annex XII - Benefit assessment of pharmaceuticals with new active substances according to Section 35a SGB V Dulaglutide (Renewed benefit assessment based on new scientific evidence according to Section 13: Type 2 diabetes mellitus), 2020.

[3] Güthlin C, Köhler S & Dieckelmann M. 2020. Chronisch krank sein in Deutschland (Being chronically ill in Germany): Zahlen, Fakten und Versorgungserfahrungen. (Facts, figures, and experiences of care.) Frankfurt/Main, Germany: Goethe University, Frankfurt am Main, Institute of General Practice.

[4] Federal Joint Committee, Statement of the full-time impartial members of the Federal Joint Committee (G-BA) of 23 September 2022 on the public hearing of the Health Committee of the German Bundestag on the Federal Government's draft law: Draft Act on the Financial Stabilisation of Statutory Health Insurance (GKV-Finanzstabilisierungsgesetz – GKV Financial Stabilisation Act). BT-Drs. 20/3448, 2022.

[5] Greiner W, Witte J, Gensorowsky D, Diekmannshemke J. AMNOG-Report 2023: Das GKV-Stabilisierungsgesetz und seine Auswirkungen. (The GKV Financial Stabilisation Act and its effects.) Beiträge zur Gesundheitsökonomie und Versorgungsforschung (Contributions to health economics and healthcare research) (Volume 43), 2023.

[6] Tagespiegel Background, GKV Financial Stabilisation Act: Hecken „ nervous about care". https://background.tagesspiegel.de/gesundheit/hecken-nervoes-wegen-versorgung (accessed on 16 May 2023).

[7] Federal Joint Committee, Early benefit assessment of new pharmaceuticals 2021: G-BA sets record with 146 completed procedures.

[8] Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V., national health care guideline: type 2 diabetes, partial publication of the long version. 2nd edition, version 1, AWMF register no. nvl-001. 9 Berendes A, Ruth T, Münscher C, Potthoff F. Ergebnisbericht zum Disease Management Programm Diabetes mellitus Typ 2: der Techniker Krankenkasse in der Region Niedersachsen. (Results report on the Disease Management Programme Diabetes mellitus Type 2: of the Techniker Krankenkasse in the Lower Saxony region.) Evaluation report as of 30 September 2013, 2013.

The European HTA Regulation and its impact on Austria

PD Dr Claudia Wild | Managing Director HTA Austria – Austrian Institute for Health Technology Assessment

The European HTA Regulation (HTAR) requires that the EU member states speak with one voice in the central steering committee (Coordination Group). In highly decentralised countries such as Austria, where many reimbursement decisions are made regionally, a nationwide coordination is a prerequisite for the successful implementation of HTAR. Various initiatives have been launched over the past 15 years (national and international horizon scanning, regional and national evaluation committees) to facilitate the rational use of and access to cost-intensive therapies. The HTAR has now accelerated the legal establishment of an Austria-wide „national evaluation board".

Introduction

In autumn 2020, the European Commission announced its (then) new „Pharmaceutical Strategy for Europe", which aims to solve the obvious problem areas of „(Europe-wide) access to innovative pharmaceuticals", „availability of (especially imported) pharmaceuticals" and „affordability of new pharmaceuticals" (A+++: Access, Availability, Affordability). The existing legislation was first revised and presented in April 2023.[1] This is now being discussed in the European Parliament and the Council. In this context, the creation of a „European medicines infrastructure" is also being discussed to counter market failure throughout the entire life cycle of a pharmaceutical (research, development, production, and distribution).[2]

As a further element, the EU HTA Regulation (HTAR) came into force in January 2022,[3] which – after a transitional phase of three years – must be implemented in a legally binding manner from 2025: oncology products and advanced therapies (ATMPs) will be assessed jointly from 2025 to 2028. The HTAR primarily regulates cooperation between European HTA institutions in the assessment of pharmaceuticals and medical devices. The aim is to pool HTA resources across Europe to develop high-quality and timely scientific assessments and thus support evidence-based decision-making at national level. This should facilitate earlier access to „real" innovations. In addition to efficiency gains in the preparation of assessments of pharmaceuticals, transparency, and traceability in the preparation of assessments should also be ensured by harmonising the methodology at a high-quality level.

Expected benefits of HTAR in small countries

The expected benefit for decision-makers in the EU Member States is that scientific reports will become available in a timely manner (at the same time as the EMA assessment)

to support evidence-based decision-making at national level. This advantage is seen above all by small countries such as Austria (which has also been highly active in EUnetHTA for years), but also Belgium, the Netherlands etc. However, during the HTAR negotiations there was resistance to this by those countries that have large independent HTA institutions (Germany, France) and will need to reorganise their processes.

The realisation of efficiency gains through reduced workload can currently only be speculated upon: however, since economic evaluations and systemic-organisational implications (such as the location of administration, qualification of personnel) are exempted from European assessments, the work content in national HTA institutions, as well as in market access departments of pharmaceutical manufacturers, will have to focus on these aspects. The European assessments must in any case be used for national decision-making (mandatory), duplication is to be excluded, but adaptations to national circumstances are possible.

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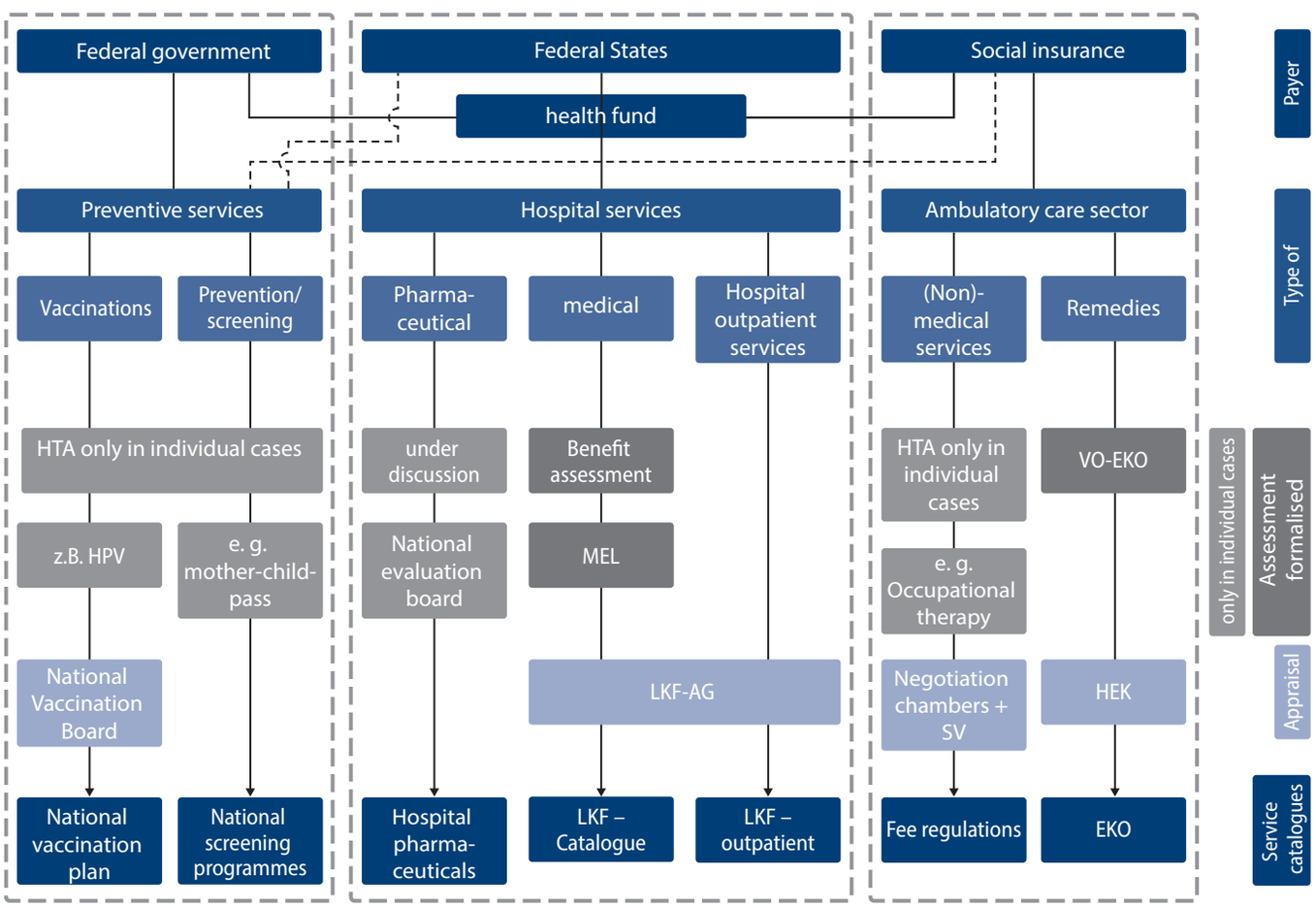
Decentralised decisions in federal states, HTA (sometimes) as a basis

Although the HTAR does not directly interfere with national reimbursement decisions, but it assumes that the member states will contribute their priorities for product evaluation in the central steering committee (Coordination Group) and speak with one voice there. In highly decentralised countries such as Austria, where many decisions are made regionally, but where the needs for health policy decisions also arise regionally, Austria-wide coordination is a prerequisite for the successful implementation of HTAR (figure 1). As some kind of patient tourism between the nine federal states has been observed due to the regional differences in reimbursement policies for particularly expensive therapies (e.g. neuro-paediatric therapies such as Nusinersen), there have been discussions for some time about the Austria-wide financing of such therapies from a joint „innovation fund". A joint decision is also a prerequisite for an active (rather than mere observer) role in the BeNeLuxA (IR) network.

To date, and in contrast to other countries, the systematic evaluation of the actual benefit of medical services using methodological HTA standards prior to the provision of these services in standard care has not been laid down in statutory regulations. Nevertheless, there are formalized processes for assessments (such as benefit assessments) prior to the decision on the inclusion of services in two cases, namely for pharmaceuticals in outpatient care and for individual medical services in the hospital sector.[4]

A pharmacological, medical-therapeutic and economic evaluation is provided for in a statutory regulation for the provision of pharmaceuticals in the community-based sec-

Control processes and benefits catalogues in the Austrian healthcare system



EKO: Reimbursement Code; HEK: Therapeutic Products Evaluation Commission; LKF: Performance-orientated hospital financing; LKF-AG: LKF working group; MEL: individual medical service; VO-EKO: Regulation Reimbursement Code (regulates pharmacological, medical and "economic evaluation" of the pharmaceuticals applied for

Source : [4]

Figure 1: In highly decentralised countries such as Austria, a nationwide coordination is a prerequisite for the successful implementation of HTAR.

tor before a pharmaceutical is included in the reimbursement codex (EKO); however, the evaluation stipulated in the regulation does not specify HTA as such and therefore no methodological HTA standards are specified. Moreover,

the assessments conducted are not publicly accessible, which contradicts a basic principle of HTA. The economic evaluation outlined in the regulation for pharmaceutical assessment primarily corresponds to a price comparison according to the specified criteria. Only in a few defined cases is an economic evaluation as understood in the HTA context (namely in the sense of a comparative cost-effectiveness analysis) provided for.[5]

However, the use of HTA shall generally be promoted in accordance with Art. 15a of the Federal Constitutional Law on Health Target Control, and the use of Health Technology Assessment (HTA), evidence-based medicine (EBM) and evidence-based public health (EbPH) is to be further promoted in accordance with Art. 12 Para. 1 No. 4 of the agreement pursuant to Art. 15a of the Federal Constitutional Law on Health Target Control. These methods contribute to evidence-based, transparent and patient-benefit-oriented decisions in the healthcare system and shall be used in particular for therapeutic, diagnostic, organisational, and public health interventions".[4]

Excursus: supply of oncology products in Austria

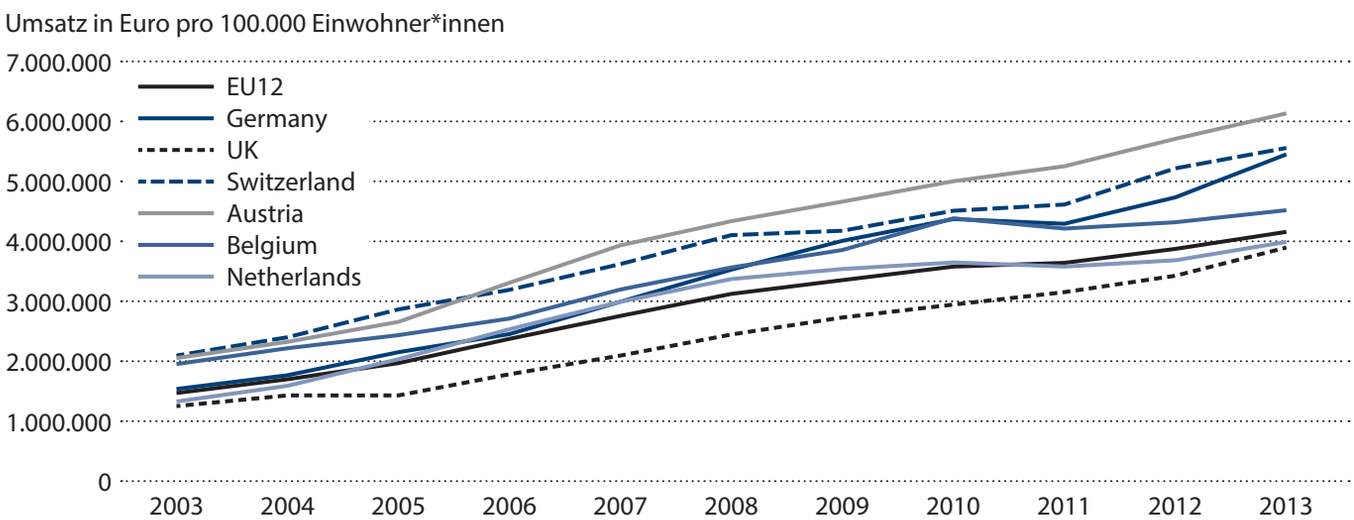
Not only does Austria – like Germany – offer rapid access to cost-intensive oncological therapies,[6] it also has an extremely generous use of pharmaceuticals compared to other European countries (figures 2 and 3). This may be praised as „cutting-edge" medical care at the highest level or criticised as the uncritical use of resources raised in solidarity. In any case, the fact is that oncological care is at a high level but varies from region to region, there is no transparency in the decisions of the regional pharmaceutical commissions and, as a result, it must be assumed that – due to small-scale reimbursement decisions – the demand pressure on regional oncologists is high.

Policies for dealing with high-priced pharmaceuticals

Various policies to deal with the high consumption of oncology products have been implemented in the last two decades.

- A „Horizon Scanning in Oncology System (HSO)" has been developed and processed since 2009 to support decision-making by (regional) pharmaceutical commissions and payers. As part of the HSO project, early assessments (n=91) of selected new oncology products were prepared by the end of 2019, for which significant financial and/or therapeutic consequences were presumed. Due to the changing European environment (EUnetHTA, BeNeLuxA), fact sheets on all new cancer pharmacotherapies have been prepared on a monthly basis since 2020. Since 2015, the pharmaceuticals have also been assessed using the ESMO scale (MCBS) according to „Magnitude of Clinical Benefit" (figure 4).[9,10] To date (March 2024), 167 factsheets have been published. The intention was and still is to promote a more evidence-based rational supply of pharmaceuticals.
- In 2016, Austria co-founded the BeNeLuxaA(IR) initiative, which aims to achieve sustainable access to high-quality treatments and their appropriate use in the participating countries. The access shall be achieved by justifying larger markets in price negotiations. The partner countries are Belgium, the Netherlands, Luxembourg, Ireland, and Austria (combined population of 43.7 million) (https://beneluxa.org/).
- The need for equal access to (effective) pharmaceuticals throughout Austria, supported by recommendations from a national pharmaceutical assessment board, has long been discussed. Such a board was piloted in 2020 and shall now be implemented in autumn 2024. The legal basis is the „Agreement pursuant to Art. 15a B-VG on the organisation and financing of the healthcare system", which was negotiated in 2023 as part of the finan-

Volume consumption of oncological therapeutics in two periods (2003-2013) and 2021



Source: [7]

Figure 2: Austria – like Germany – not only provides rapid access to cost-intensive oncological therapies, but also uses them widely, which is reflected in the comparative volume consumption (2003-2013).

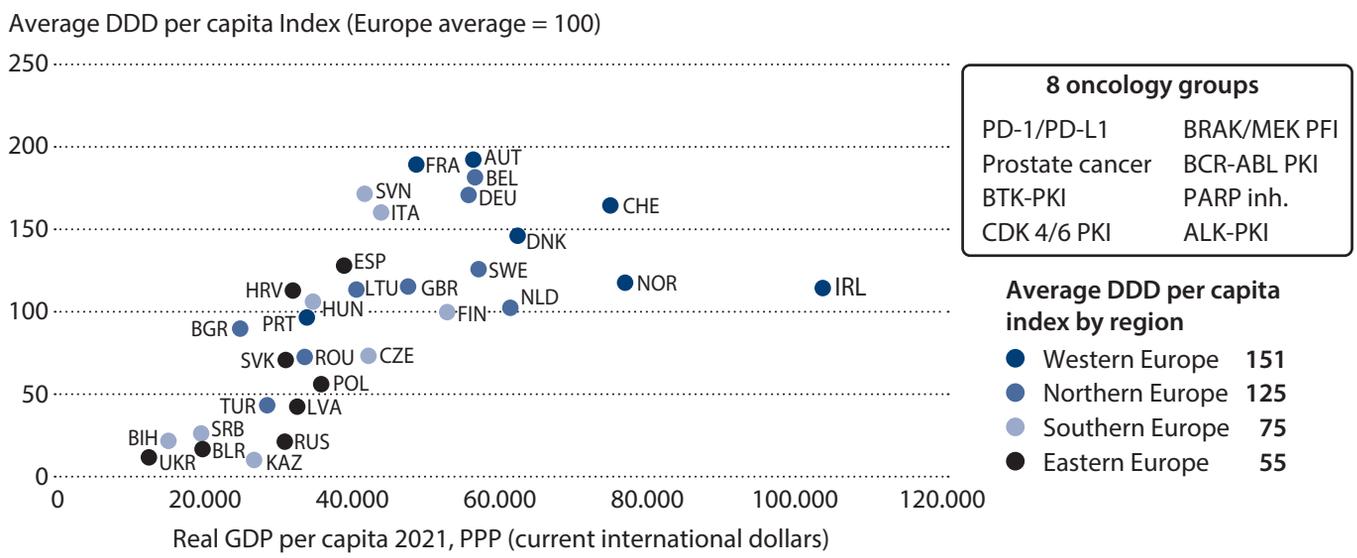
cial equalisation negotiations.[11] The specific structure will be presented in the form of rules of procedure at the end of June 2024. Some key points (the office is located in the ministry, the national assessments based on the EU JCA will be carried out by the AIHTA for hospital pharmaceuticals, by the umbrella organisation of social insurance companies for the private practice sector, the appraisal will be carried out by the evaluation board and will result in recommendations on the application algorithm/application rules) are already known, others are still pending (patient involvement, financing of individual therapies through innovation funds).

- In autumn 2022, Austria joined the transnational International Horizon Scanning Initiative (IHSI) (https://ihsi-health.org/), which has set itself the task of promoting fair and transparent pharmaceutical prices, to facilitate the identification of those pharmaceuticals that are to be regulated. IHSI is funded by nine European countries (the Netherlands, Ireland, Switzerland, Denmark, Portugal, Norway, Belgium, Sweden, and Austria) and implemented by the US Emergency Care Research Institute (ECRI).

Conclusion: impact of HTAR on Austria

For the implementation of the HTAR and thus the use of the European JCA and its integration in Austrian treatment pathways, better coordination of information requirements and the establishment of a national evaluation board for the creation of application algorithms is essential. Coordination at the „lowest" level is already taking place through the networking of the relevant departments of the hospital providers and the registration and joint pro-

Volume consumption of oncological therapeutics in selected countries



Source: [8]

Figure 3: Despite early assessments of new oncology products to support decision-making in regional pharmaceutical commissions, Austria is still the European champion in the volume consumption of cost-intensive oncological therapies (2021).

cessing of new controversial topics (pharmaceuticals, medical devices, IT/AI applications). The effects of patient tourism for expensive therapies, totally different use of expensive therapies in the nine federal states, inability to actively participate in BeNeLuxA (IR) and, most recently, the HTAR have accelerated the political decision and legal anchoring of a national evaluation board. The result of the implementation is still pending and can only be assessed in one to two years' time.

Reverences

[1] Proposal for a Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency. com_2023_193_1_act_en.pdf (europa.eu)

[2] European Parliamentary Research Service (EPRS) Scientific Foresight Unit (STOA) European pharmaceutical R&D: could public infrastructure overcome market failure? PE 697.197 Dec 2021. https://go.sn.pub/6yn2ib.

[3] EU Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. https://go.sn.pub/ZeUQQk

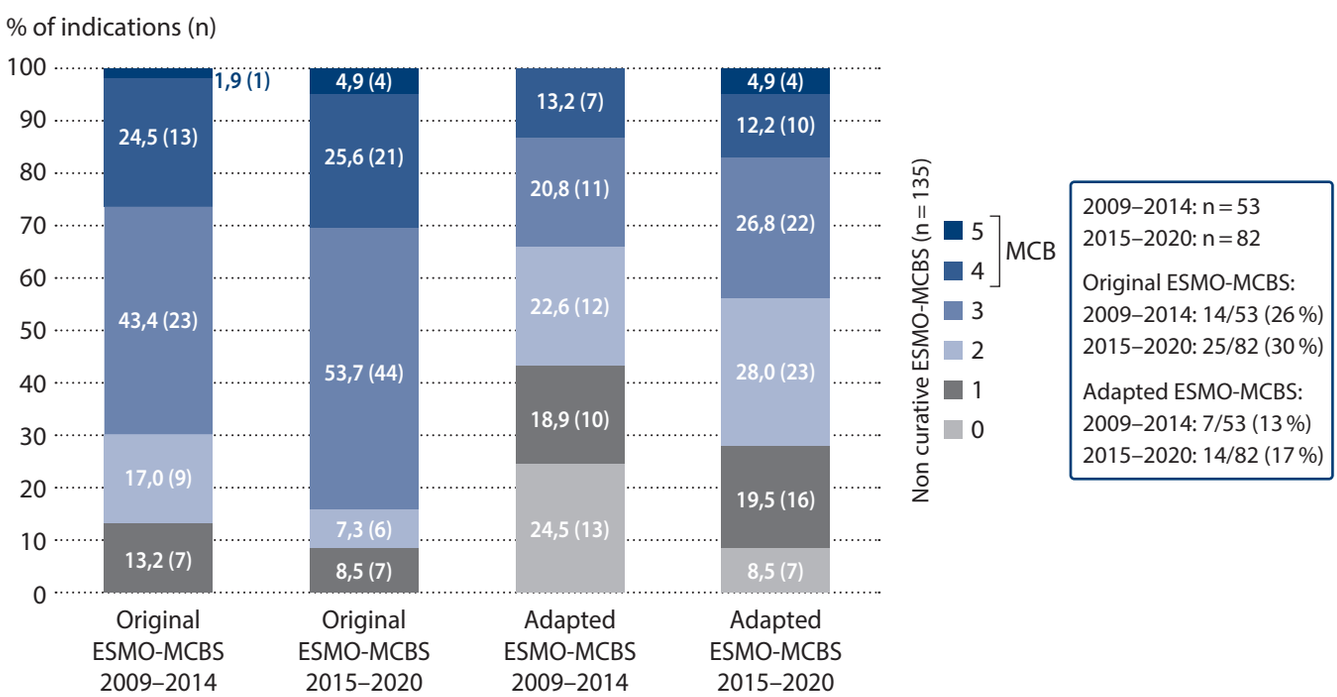
[4] Wild C, Zechmeister-Koss I (2023) HTA in Österreich (HTA in Austria). In: Perleth M, Busse R, Gerhardus A, Gibis B, Lühmann D, (Eds.). Health-Technology-Assessment Konzepte, Methoden, Praxis für Wissenschaft und Entscheidungsfindung (Health Technology Assessment Concepts, Methods, Practice for Science and Decision Making). 3rd updated and expanded edition ed. Berlin: Med. Wiss. Verl.-Ges.

[5] Zechmeister-Koss I, Stanak M, Wolf S (2019) The Status of Health Economic Evaluation within decision making in Austria. Vienna Medical Weekly 2019;169:271–283.

[6] Uyl-de Groot C, Heine R, Krol M, Verweij J (2020) Unequal Access to Newly Registered Cancer Drugs leads to Potential Loss of Life-Years in Europe. In: Cancers, 12 (8):2313.

[7] Jönsson B, Persson U, Wilking N (2016) Innovative treatments for cancer in

Comparison of ESMO "Meaningful Clinical Benefit Scores" (MCBS) in two approval periods (2009-14, 2015-20)



Source: [9, 10]

Figure 4: Since 2015, pharmaceuticals have also been assessed using the ESMO scale according to „Magnitude of Clinical Benefit" to support decision-making by (regional) pharmaceutical commissions and payers.

Europe - Value, cost and access. IHE Report 2016:2. https://go.sn.pub/qz8d30

[8] IQVIA (2023) Global Oncology Trends 2023, Outlook to 2027, https://go.sn.pub/avp5mt

[9] Grössmann N, Del Paggio JC, Wolf S, Sullivan R, Booth CM, Rosian K, Emprechtinger R, Wild C (2017) Five years of EMA-approved systemic cancer therapies for solid tumours – a comparison of two thresholds for meaningful clinical benefit. European Journal of Cancer 82C, pp. 66-71.

[10] Grössmann N, Rothschedl E, Wolf S, Wild C (2021) 12-years of European cancer drug approval – a systematic investigation of the magnitude of clinical benefit, Annals of Oncology. June 01. https://doi.org/10.1016/j.esmoop.2021.100166.

[11] Government bill „Agreement pursuant to Art. 15a B-VG on the organisation and financing of the healthcare system" (2023) with enclosure, https://go.sn.pub/or7wer and https://go.sn.pub/tcnfq2

Status of the Registry Act – relevance for authorisation and benefit assessment

Markus Algermissen, Jana Holland, Sarah Kosecki | Federal Ministry of Health

Medical registries offer significant added value for quality assurance in healthcare and research. The future Registry Act aims to better use this potential by establishing a foundation for greater transparency across the registry landscape, supporting the further development of medical registries' quality, and creating more opportunities for the use of registry data, particularly their linkage. These new structures could ultimately help ensure that registries are more closely involved in authorisation and benefit assessment processes.

The spring meeting 2024 of the Interdisciplinary Platform on Benefit Assessment focused on the interplay between authorisation and benefit assessment. The final presentation dealt with the status of the planned Registry Act and its relevance for authorisation and benefit assessment.

One key insight is that medical registries can offer substantial added value for quality assurance in care and research, especially where randomised controlled trials (RCTs) face ethical and/or pragmatic limitations or where the transferability of study results to everyday clinical care is crucial. However, medical registries and those using registry data for research and healthcare face various hurdles. The planned Registry Act aims to address these challenges.

It is part of the digitalisation strategy for health and care from March 2023, promoting sustainable structures for medical registries. The main goal is to improve the availability of registry data and network it with other data. The potential of electronic patient records in relation to medical registries will also be considered.

The Health Data Use Act, which came into force on 26 March 2023, has already made significant strides toward a „networked health data ecosystem" with a decentralised research data infrastructure. The planned Registry Act continues along this path (figure 1).

What is the current situation for medical registries and what are the objectives of the Registry Act? The landscape of medical registries is highly heterogeneous, with significant differences in duration, size, and objectives. Assessing the quality of individual registries is often challenging, complicating the identification of suitable registries for projects and public sector allocation decisions.

Until the publication of the registry report in 2021, commissioned by the Federal Ministry of Health (BMG) and pre-

pared by the BQS Institute for Quality & Patient Safety GmbH and the Technology and Methods Platform for Networked Medical Research e. V.,[1] there was a lack of transparency regarding Germany's medical registry landscape. The report provided an initial solution by systematically analysing the landscape in a database, further developed into a web-based registry directory (see https://registersuche.bqs.de/) ensuring that the entries are more up-to-date and accessible. Germany has over 400 medical registries, most lacking specialised legal bases (unlike the implant registry or state cancer registries, which were established on the basis of special laws).

Moreover, many of the registries that are not regulated by special legislation are confronted with legal uncertainties. They collect personal data on the basis of general data protection legislation and therefore operate in a heterogeneous network of standards under EU, federal, and state law. This creates legal uncertainties for transnational data processing in these registries, further complicated by inconsistent interpretations of data protection regulations by supervisory authorities (figure 2).

The Registry Act, currently in draft, intends to address these needs. Creating more transparency about the medical registry landscape is sensible. Identifying potentially

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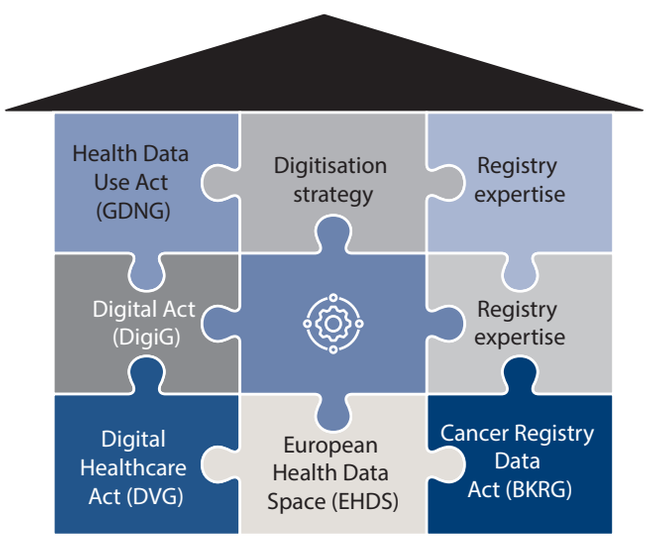
The Registry Act as part of various digitisation initiatives in the healthcare sector



Source: Federal Ministry of Health

Figure 1: The planned Registry Act is intended to continue the path towards a „networked health data ecosystem" with a decentralized research data infrastructure.

relevant data sources is fundamental for further utilisation and networking. A registry directory, similar to https://registersuche.bqs.de/, could be established. Entry in the directory would be voluntary for the medical registries.

To better realise their potential, medical registries should meet certain quality requirements. A voluntary qualification process could allow registries to have their quality and usability validated or further developed and recorded for interested users. Registries already have to carry out extensive review processes (including data protection and ethics reviews) in order to be set up.

To avoid excessive bureaucracy, the qualification process should build on existing checks. This is particularly important in view of the heterogeneity of the medical registry landscape with some privately organised and financed registry structures, a high level of intrinsic motivation on the part of registry operators and little public funding. This also raises the question of why registries should undergo a qualification process. The qualification process could be motivated by the intrinsic desire for further development and potentially linked to simplifications in data processing.

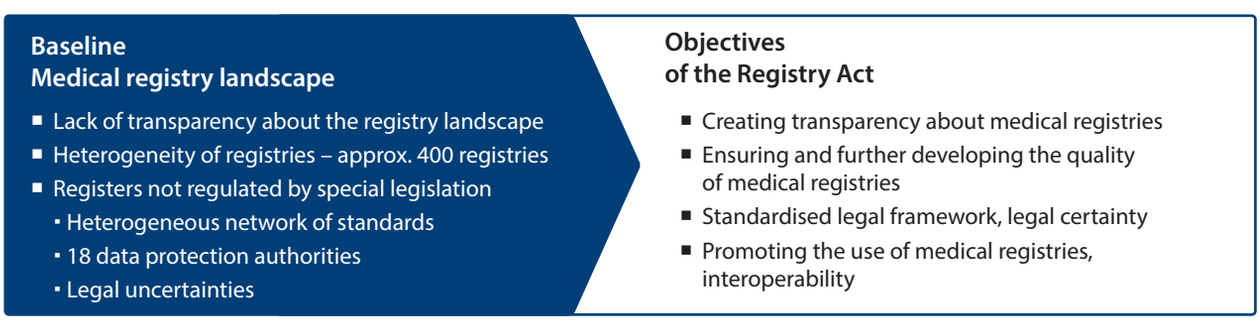
This would support medical registries, create more legal certainty, and make registry data more usable for research and healthcare. For example, the data processing of successfully qualified registries could follow the Registry Act's provisions, possibly allowing data collection with patients' right to object under certain conditions, without requiring informed consent.

The Registry Act aims to create a nationwide legal framework, enabling qualified registries to link their data through collaborations. The gradual introduction of a research code, as envisaged in the digitalisation strategy, could be promoted. The core of this consideration could be the creation of a regulation that explicitly allows all registries to collect the health insurance number and store it in their trust centres.

To create transparency about the medical registry landscape, further develop its quality and implement possible simplifications in the processing of registry data, it must be regulated how the underlying processes are implemented institutionally. The registry report[2] recommends establishing a central office for medical registries (ZMR) to provide guidance, service, and advice, promoting networking among registries and stakeholders, without operating registries itself.

As part of a decentralised registry research data infrastructure, the ZMR should also promote European connec-

Current situation of the medical registry landscape and objectives of the Registry Act



Source: Federal Ministry of Health

Figure 2: Many of the registries that are not regulated by special legislation face legal uncertainties. They collect personal data based on general data protection legislation and therefore operate in a heterogeneous network of standards under EU, federal, and state law.

tions within the European Health Data Space. Regarding the implementation of such a consideration, questions about the location and the least bureaucratic organisation possible need to be discussed.

Promoting the use of registry data requires supporting registries and researchers in conducting high-quality registry-based studies. For example, registries could address relevant healthcare questions, such as the importance of a new pharmaceutical in healthcare if other new pharmaceuticals are also authorized in the same therapeutic area.

Since February, the BMG has funded a research project on registry-based intervention studies in Germany (REGINT), involving the German Network for Health Services Research, the Institute for Biometry and Registry Research at Brandenburg Medical School, the Association of German Tumour Centres, and the Centre for Evidence-based Healthcare at the Technical University of Dresden's Medical Faculty. This project aims to identify obstacles and develop recommendations for suitable framework conditions for registry-based intervention studies, which could be incorporated into the planned Registry Law.

This could also take into account the fact that the law does not currently clearly regulate the extent to which pharmaceuticals that are generally reimbursable may also be prescribed at the expense of the statutory healthcare system if they are used in an authorised area of application as part of a healthcare-related study.

Medical registries need an established place in our networked healthcare data ecosystem. The future Registry Law aims to create the foundation for more transparency across the registry landscape, further develop the quality of medical registries, and provide more options for utilising registry data, particularly their linkage. These new structures could enable institutions like the Federal Joint Committee and the Institute for Quality and Efficiency in Health Care to integrate registries more closely into their processes.

References

[1] Niemeyer A et al (2021): Gutachten zur Weiterentwicklung medizinischer Register zur Verbesserung der Dateneinspeisung und -anschlussfähigkeit im Auftrag des Bundesministeriums für Gesundheit (BMG). (Expert report on the further development of medical registries to improve data feed-in and connectivity on behalf of the Federal Ministry of Health (BMG)). https://go.sn.pub/8b9jXJ. Accessed on 24 March 2022

[2] Ibid.

More speed and solid evidence? Interaction between marketing authorisation and HTA is open

Florian Staeck

The future relationship between regulatory approval and health technology assessment (HTA) is currently marked by a productive tension among regulatory authorities, HTA organisations, and payers. It remains unclear which approach will prove more successful: A „closer alignment" of the processes of approval and HTA, or the deliberate separation of these procedural steps. This tension arises from the desire for high safety of new pharmaceuticals, high certainty of evidence, and rapid research and market introduction. These issues were discussed by participants at the 19th meeting of the Interdisciplinary Platform for Health Technology Assessment, held in Berlin in mid-March 2024 under the general theme: „Interaction between HTA and authorisation."

The backdrop to this discussion is the trend towards increasingly early approvals of new pharmaceuticals based on „immature" evidence, driven largely by the US Food and Drug Administration (FDA), which grants approvals based on „pragmatic" trials. Participants in the discussion were convinced that this trend will spill over into Europe, compounded by the fact that European pharmaceutical legislation also aims at acceleration, streamlining, and shortening of deadlines. However, this drive for faster approvals conflicts with the pursuit of the highest possible evidence and patient safety, given the lack of sufficient long-term data.

Another driver of this development is the different environments in which the FDA and the European Medicines Agency (EMA) operate. The FDA must regularly justify its actions before the US Congress and has incorporated patient preferences into its decisions much earlier than the EMA. By contrast, the EMA operates in a scientifically based „remote" mode. Unlike in Europe, there is no HTA procedure in the US as discussed at the EU level – making the FDA the primary hurdle to market access. Additionally, in Germany, the self-governance bodies, such as the Federal Joint Committee (G-BA) and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband), act as a „firewall" between industry and politics – something that does not exist in the US, participants noted.

Both perspectives have come closer together

However, this trend has also reached the EMA. Fifteen years ago, the taboo in the relevant CHMP Committee (Committee for Human Medicinal Products) was never to talk about HTA – this is no longer the case, participants familiar with the matter reported. Similarly, in Germany, the perspectives of the Federal Institute for Drugs and Medical Devices (BfArM) and the G-BA have now come closer together through joint consultations.

However, the conference highlighted different emphases regarding the relationship between licensing and HTA. Over the next ten years, 70% of all new marketing authorisation applications would be expected in the fields of oncology and central nervous system (CNS). New assessment methods and high evidence standards would be essential here. Otherwise, there could be unbridgeable gaps because the controlled conditions in approval studies increasingly diverge from real-world care. Moreover, it is becoming more challenging to maintain randomised controlled study conditions in increasingly finely differentiated indication areas.

This was taken as an opportunity to call for scientific support to explore the limits of real-world evidence. Other participants questioned who could provide the necessary personnel, as the relevant department within the European Commission's Directorate-General for Health and Food Safety (DG SANTE), tasked with implementing the EU

HTA Regulation, currently has only five staff members.

Voices at the conference were also sceptical regarding the different contextual preferences and value systems in regulatory approval and HTA. This is because marketing authorisation is about managing the benefits and risks of a new active substance – the corresponding preparation is often tested against placebo for this purpose. Benefit assessment, on the other hand, examines whether a new pharmaceutical improves existing care. Linking the two steps could thus result in the standards for authorisation being tightened. This could argue in favour of keeping the two processes separate, as the objectives are simply too different, it was said.

These developments are accompanied by ongoing uncertainties in the run-up to the start of the EU benefit assessment, participants emphasised. In particular, reference was made to the Implementing Act on the exchange of information between the EMA and the EU HTA Coordination Group, which was not yet available at the time of the conference in March 2024. A multitude of changes would be needed in advance – for example regarding the G-BA's rules of procedure or the module templates in the context of early benefit assessment. However, not all tasks need to be completed by 12 January 2025. In fact, there is time for this until the results of the first assessment as part of the EU HTA procedure are available and the national AMNOG procedure follows, it was explained.

Precisely for this reason, there is great methodological uncertainty, as it is still not really foreseeable how large the „delta" between the EU assessment and the national early benefit assessment will likely be. If certain core elements of the AMNOG are not reflected in the joint clinical assessments, this could mean that a large part of the EU assessment cannot be used for the G-BA process. Participants pointed out that test runs for the PICO determination (PICO stands for Patient, Intervention, Comparison, and Outcome) had shown how far the methodological ideas at EU level still differ.

Half a dozen PICOs – that is not feasible

The option for the pharmaceutical company to make redactions in the assessment report was seen as highly critical. This was described as a „no go", as it involved aggregated data sets. Other participants warned that the corresponding guidance documents allowed member states to pick and choose the „appropriate" methodological elements. In clinical trials, however, it is not feasible to run half a dozen – or even more – PICOs in parallel; the definition of „lead PICOs" would be necessary here.

These other aspects were also discussed at the conference, some of them controversially:

- **Impact of the future EU HTA process on „small" EU member states:** The planned assessment will have a variety of consequences for both smaller and economically weaker member states. Participants emphasised that what was standard treatment in Germany five or six years ago could represent the current state-of-the-art of treatment in other EU member states. Many neighbouring countries are following AMNOG with great interest but cannot implement it in their healthcare systems due to personnel constraints. This is especially true in countries with strong federal structures, where decisions on pharmaceutical pricing agreements are made at the level of federal states or comparable entities.

The smaller the level at which reimbursement decisions are made, the greater the risk of „lobbying susceptibility" – regardless of the evidence of the additional benefit of a new therapy, it was noted. Against the backdrop of the EU HTA procedure, a nationwide evaluation board has been established in Austria, for example, which is due to start

work in autumn 2024. Experts there hope that this will lead to a stronger evidence-based approach when deciding whether and at what price a new pharmaceutical should be reimbursed.

- **Ongoing challenges in evaluating new pharmaceuticals for chronic diseases:** Participants pointed out that the GKV Financial Stabilisation Act had worsened the framework conditions for clinical studies for chronic diseases. This applies in particular to new pharmaceuticals, which generally bring incremental advances in therapy. The downgrading of a minor or non-quantifiable additional benefit disproportionately affects new pharmaceuticals for chronic diseases, such as antidiabetics. Only 2% of previous AMNOG procedures have seen the G-BA grant a significant or considerable additional benefit to a new diabetes pharmaceutical. In oncology, however, this applies to 30% of all procedures.

The long duration of clinical studies for chronic diseases is also typical. For example, cardiovascular outcome studies can last up to 615 days, with an additional lead time of one to two years. This could mean that the comparator is no longer part of current care when the pharmaceutical company submits its dossier. Discussion participants made it clear, however, that it is not possible to deviate from the current standard of care in the AMNOG process – this requirement is regulated by law. Thus, it remained unclear how the fact of long study duration could be taken into account in pricing.

- **Opportunities and challenges of a law on medical registries:** The Registry Act, which is already provided for in the coalition agreement of the coalition parties, could be seen as the „little sister" of the Health Data Use Act, it was said. The starting point for this is the currently heterogeneous landscape of over 400 registries in Germany. There has so far been a lack of transparency regarding the quality of the respective data collections. As a result, it is currently not possible to adequately assess the contribution that individual registries make to improving care. A framework law is planned that would target those registries that are not already covered by special legislation – such as the cancer registries.

According to considerations by the Federal Ministry of Health (BMG) – a draft bill was not yet available at the time of the platform meeting – a central office is planned to serve as a guide and service function for registries and to ensure their integration into the European Health Data Space. Interoperability regulations should also enable registries to exchange data with each other. The goal of this planned process is to have networked registries in the future, forming part of a health data ecosystem.

These new structures could then put the G-BA or IQWiG in a better position in future to incorporate registry data more strongly into their own processes, such as benefit assessments. From this heterogeneous mix, it became clear that this is a long-term process with an uncertain outcome.

Participants had a lively discussion about the status of registry data compared to data collections in the electronic health record (EHR). It was argued that registry data comes from an analogue process, whereas what is known about a patient will in future be found in the EHR. The resulting consideration was whether, in future, registries will be nothing more than structured derivations from the EHR. This was met with criticism.

Registries, it was said, are scientific documentation. In contrast, patient-centred data would be collected in the EHR, in which the confounders could not be identified in order to derive a scientific evaluation from them. The discussion made it clear that the future coexistence or parallel existence of registries and the EHR has not yet been conclusively clarified. However, there was a desire

that a legal regulation for registries should be formulated in a technology-neutral way to accommodate future developments in digital health data ecosystems.

It was implicitly clear to the participants that a functioning EHR does not yet exist, as major problems in the information technology of practice management systems still await a practical solution that must also function in regular operation.

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